THE PREPARATION OF N-METHYL-MENTHYLAMINES ETC. BY MEANS OF A NEW METHOD OF N-ALKYLATION AND A POSSIBLE METHOD OF DETERMINING THE EFFECTS OF SUBSTITUTION BY MEANS OF THE VELOCITY OF DECOLORISATION OF SUBSTITUTED PYRIDINES-ARYLIMINES

James A. Hendry

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THE PREPARATION OF N-METHYL-MENTHYLAMINES ETC. BY MEANS OF A NEW METHOD OF N-ALKYLATION

and

A POSSIBLE METHOD OF DETERMINING THE EFFECTS OF SUBSTITUTION BY MEANS OF THE VELOCITY OF DECOLORISATION OF SUBSTITUTED PYRIDINE-ARYLIMINES.

being a thesis

presented by

JAMES A. HENDRY, B.Sc.,

to the

UNIVERSITY OF SAINT ANDREWS

in application for

the

DEGREE OF DOCTOR OF PHILOSOPHY.

DECLARATION.

I hereby declare the following Thesis to be a record of results of experiments carried out by me and furthermore that the Thesis is of my own composition and has not been previously presented in application for a Higher Degree.

The investigations comprising Part I of this Thesis were conducted in the Chemical Research Laboratory of the United College under the direction of Professor John Read, M.A., Sc.D., Ph.D., F.R.S.. The research described in Part II was carried out in the Chemisches Laboratorium der Friedrich=Schiller=Universität, Jena under the direction of the late Professor Dr. Wilhelm Schneider.

31st July, 1940.

CERTIFICATE.

I hereby certify that James A. Hendry, B.Sc., has spent eight terms at research work under my direction in conformity with the conditions of Ordinance No.16 (St. Andrews), that he spent a year conducting organic chemical research work at the University of Jena, and that I approve of his submission of the accompanying Thesis in application for the Degree of Ph.D..

August 2nd, 1940.

Director of Research.

UNIVERSITY CAREER and RESEARCH EXPERIENCE.

I entered the United College, University of St. Andrews, in October, 1932, graduating B.Sc. in June, 1935. In July, 1935, I was awarded an Exchange Scholarship for study in Germany by the University of St. Andrews, which I utilised during Session 1935-36 to study organic chemistry at the University of Jena. Returning to St. Andrews in October, 1936, I read for the B.Sc. Honours Degree in Chemistry and subsequently obtained the post-graduate degree of B.Sc. with First Class Honours in Chemistry in June, 1937.

In July, 1937, I was awarded a Carnegie Research Scholarship which I held for one year. In July, 1938, I was awarded a Hanseatic Scholarship for research in Germany, which I conducted at the University of Jena. On returning to this country on the outbreak of war my Carnegie Scholarship was renewed for a further year and I resumed my research work at the University of St. Andrews.

The researches described in this Thesis therefore cover the period from September, 1937, till July, 1940.

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Part I.

THE PREPARATION OF N-METHYL-MENTHYLAMINES ETC.

BY MEANS OF A NEW METHOD OF N-ALKYLATION.

A. INTRODUCTION.

Alkylation may be defined as the introduction of an alkyl radical by substitution or addition into the molecule of an organic compound. The introduction of an aralkyl radical, such as benzyl, is also included under this heading. Alkylation may be divided into five general types according to the linkages effected, namely:-

(1) Substitution for hydrogen in the hydroxyl group of an alcohol or a phenol, the alkyl group being bound to oxygen.

(2) Substitution for hydrogen attached to nitrogen, where the alkyl group is bound to trivalent nitrogen.

(3) Addition of an alkyl halide or an alkyl ester to a tertiary nitrogen compound. In this case the alkyl is again attached directly to the nitrogen atom, which now however engages four valency bonds and becomes the seat of a positive charge.

(4) Substitution for hydrogen in carbon compounds, the carbon of the alkyl group being bound to the carbon of either aliphatic or aromatic compounds. If an

aromatic hydrogen is substituted the alkylation is called nuclear alkylation. Both are examples of carbon to carbon alkylation.

(5) Direct linkage of alkyl to a metal, as in alkyl-metallic compounds.

Alkylation is of the utmost importance in organic chemistry, both in the laboratory and in industry. Thus one or other of the types of alkylation outlined above is continually being met with in the preparation of such varied substances as anaesthetics, antipyretics, alkaloids, antiseptics, dyes, explosives, flavours, hypnotics, intermediaries, perfumes, photographic chemicals, plastics, rubber accelerators, solvents, soporifics, gasoline, etc..

The reagents used to bring about alkylation are known as alkylating agents. These may be summarised briefly under the following headings:-

(a) Alcohols.

Alcohols are employed as alkylating agents chiefly in technical processes, largely as a result of their availability at low cost. Suitable catalysts are required in practically every case and excellent yields are obtained. For example, dimethylaniline is

prepared from aniline and methanol in the presence of a small amount of sulphuric acid, while diethylaniline is made from aniline and ethanol using hydrochloric acid as catalyst. The lower alcohols are now commonly used for the catalytic vapour-phase synthesis of alkylamines and for the alkylation of phenols.

(b) Alkyl halides.

Alkyl halides are employed extensively in the laboratory as alkylating agents. The lower members of the series are now available at low cost, owing to modern methods relating to the addition of hydrochloric acid to olefines and the dehydrochlorination of polychlorinated paraffins. Ethyl chloride, for instance, is used extensively for various types of alkylation, including the preparation of diethylamine, the carbon to carbon alkylation involved in the manufacture of barbital and for the preparation of alkylated metals such as lead tetraethyl. Methyl and ethyl bromides and iodides are among the commonest alkylating agents known. They react easily and are used in the preparation of drugs, medicinal chemicals, simple and mixed ethers and for the alkylation of phenols and amines.

(c) Alkyl sulphates.

Dimethyl sulphate and diethyl sulphate are now widely employed as alkylating agents, in the presence of alkali. Dimethyl sulphate is used extensively for methylation leading to alkyl-oxygen and alkyl-nitrogen compounds. Diethyl sulphate does not react so readily as dimethyl sulphate. In an anhydrous medium, however, both the ethyl groups can be made to react, whereas in the presence of water only one of the ethyl groups can be used for alkylation.

(d) Aralkyl halides.

Benzyl chloride is the commonest example of this type and is almost always used for the introduction of the benzyl group as in the alkylation of ethyl aniline to benzyl ethyl aniline.

(e) Arylsulphonic alkyl esters.

Methyl benzene sulphonate and methyl toluene sulphonate are used for the preparation of tetra-alkyl-ammonium compounds. According to Sekera and Marvel, (J. Am. Chem. Soc., 55, 345 [1933]), the higher alkyl (C_{10} and above) esters of p-toluene sulphonic acid and p-bromobenzene sulphonic acid are of great value as alkylating agents in the preparation of alkylamines, since they react more smoothly than the sluggish higher

alkyl halides and are obtained more easily than the higher alkyl sulphates.

In addition to these reagents, certain alkyl quaternary ammonium compounds have been employed for alkylations leading to such substances as phenetole, antipyrine, acriflavine and caffeine. Olefines, in the presence of a metallic halide or sulphuric or phosphoric acids can also take part in syntheses involving alkylation. In addition, the use of aliphatic diazo-compounds, e.g. diazo-methane, for certain types of alkylation may be mentioned.

B. THEORETICAL.

A new method of N-alkylation.

The normal methods of N-alkylation involve treatment of a primary base with dialkyl sulphates or alkyl halides. The product usually consists of a mixture of unchanged primary and secondary and tertiary bases, while the formation of even some quaternary ammonium salt may not be entirely excluded. The relative proportions of these bases in the mixture will naturally depend on the molecular concentration of the alkylating agent used, so that it is possible, by modifying the conditions of the experiment, to prepare mixtures in which the desired substance, be it the secondary or tertiary base or the corresponding quaternary ammonium salt, is in preponderance over the others. Even in such cases, however, isolation of the desired base in the pure state involves its separation from the mixture by one or other of the recognised classical methods. Treatment of the mixture with nitrous acid results in the destruction of unchanged primary base and the conversion of the secondary base present into a nitrosocompound, while the tertiary base remains unaffected by this reagent. The tertiary base can

therefore be isolated in this way, while the nitrosamine formed can also be separated and the secondary base regenerated from it by hydrolysis with a suitable hydrolysing agent. Any unchanged primary base is however lost in the process. This procedure, while quite straightforward in principle, is not so satisfactory in practice. In the case of valuable bases, loss of unreacted primary base and the poor yields so often obtained may prove a source of considerable annoyance. Moreover, unless the tertiary base so isolated can be further purified in the form of a crystalline derivative, no positive guarantee of its purity can be advanced, since it is often difficult to remove all secondary base present as nitrosamine. Only in the case of the secondary base is the method sometimes entirely satisfactory, namely in such cases where the nitrosamine is relatively stable, thus enabling it to be purified by distillation under diminished pressure, or when it is a solid at ordinary temperature and can be purified by recrystallisation. In the case of liquid amines, the latter condition is the ideal one, since the intermediate product is a solid. Even then, however, hydrolysis of the nitrosamine to the corresponding secondary base may not be too easy. When separation of the mixture of bases is

effected by means of the Hinsberg reagent, the primary base can be regenerated and recovered. This advantage is, however, offset by the fact that regeneration of the secondary base is often extremely difficult.

In spite of the difficulties indicated above, these two methods have proved of the utmost value and effect a sufficiently good separation of primary, secondary and tertiary base for most general purposes. In delicate stereochemical work, however, where complete stereochemical purity is demanded, their application is strictly limited. For such work, a more direct method of mono- and di-N-alkylation, which would eliminate the complications involved in the separation of mixtures of primary, secondary and tertiary amines, has therefore long been sought. In all organic work, but particularly in stereochemistry, the isolation and purification of intermediate compounds is essential in passing from one stage of a synthesis to another. Only in such cases can the purity of the final product be assured.

Such a method of N-alkylation has now been worked out on the basis of a recent observation by Clark and Read (J.C.S., 1934, 1775), who noticed that l-menthylglycine decomposes upon melting with the

formation of N-methyl-l-menthylamine and carbon dioxide.

$$C_{10}H_{19}\cdot NH\cdot CH_2\cdot COOH \longrightarrow C_{10}H_{19}\cdot NH\cdot CH_3 + CO_2$$

This was confirmed by Galloway (Dissertation. St. Andrews, 1935), who repeated the experiment on a larger scale. The following method was used in preparing the l-menthylglycine:-

Slightly more than two molecular proportions of l-menthylamine were condensed with one molecule of ethyl chloroacetate for three hours at 120-130°, when condensation occurred with formation of ethyl-l-menthylglycine and elimination of hydrochloric acid, which was immediately fixed by the excess primary base present, according to the equation

$$2C_{10}H_{19}\cdot NH_2 + Cl\cdot CH_2\cdot COOEt \longrightarrow C_{10}H_{19}\cdot NH\cdot CH_2\cdot COOEt + C_{10}H_{19}\cdot NH_2,HCl$$

A quantity of 5% methyl alcoholic potassium hydroxide sufficient to hydrolyse the ester and to neutralise the hydrochloric acid formed above was then added and the whole refluxed for two hours on the water-bath, when the hydrolysis was complete.

$$C_{10}H_{19}\cdot NH\cdot CH_2\cdot COOEt + C_{10}H_{19}\cdot NH_2,HCl + 2KOH \longrightarrow C_{10}H_{19}\cdot NH\cdot CH_2\cdot COOK + C_{10}H_{19}\cdot NH_2 + EtOH + KCl + H_2O$$

The alcohol and excess l-menthylamine were removed by steam-distillation and the base recovered as hydrochloride. The remaining alkaline solution was concentrated to smaller bulk, cooled in ice and carbon dioxide passed in till the solution was acid. Under these conditions, the l-menthylglycine, being the least soluble constituent of the mixture, was precipitated.

$$2C_{10}H_{19}\cdot NH\cdot CH_2\cdot COOK + CO_2 + H_2O \longrightarrow 2C_{10}H_{19}\cdot NH\cdot CH_2\cdot COOH + K_2CO_3$$

After recrystallisation the l-menthylglycine was subjected to pyrolysis at 200°, the resulting N-methyl-l-menthylamine being steam-distilled away from alkaline solution and isolated as the hydrochloride. The hydrochloride again was recrystallised up to maximum rotatory power and the free base liberated from the pure hydrochloride. The N-methyl-l-menthylamine so obtained was stereochemically pure and was characterised by Galloway in the form of its derivatives with benzoyl chloride, p-toluene-sulphonyl chloride and nitrous acid. Galloway, however, made no mention of

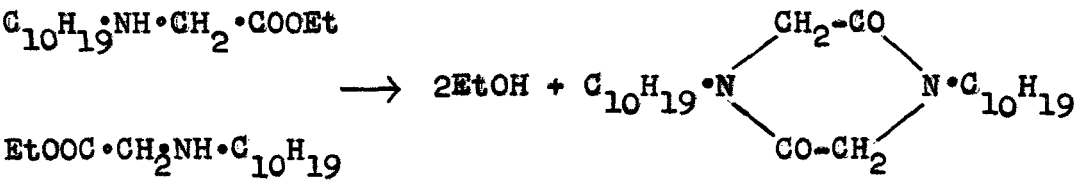
the physical constants of this secondary base.

Similarly, starting from d-neomenthylamine, Galloway succeeded in getting through to N-methyl-d-neomenthylamine by applying this method of N-alkylation. Again no physical constants have been recorded for the base, which has however been characterised by the same three derivatives as for N-methyl-l-menthylamine above. It should of course be mentioned that Galloway was mainly interested in the nitroso-compounds of these bases, from which he hoped to prepare α-methyl-l-menthylhydrazine and α-methyl-d-neomenthylhydrazine respectively, by applying the methods of Kijner and Fischer.

This work on the mono-N- methylation of l-menthylamine and d-neomenthylamine has now been repeated more exhaustively and the gaps left by Galloway have been filled in. In particular, the main physical constants of these secondary bases have been determined. It has further been shown that the method is not quite so straightforward as was at first supposed, since an important subsidiary reaction occurs at two distinct phases of the process.

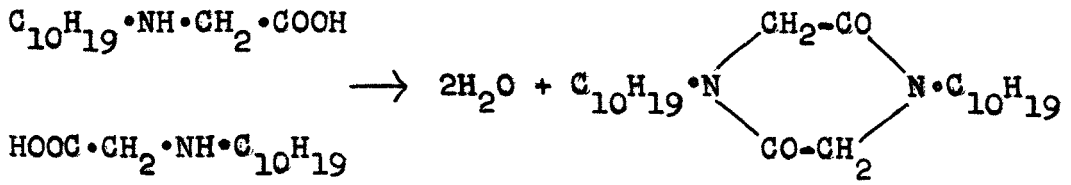
(a) The hydrolysis of ethyl-d-neomenthylglycine to d-neomenthylglycine with alcoholic potassium hydroxide

does not proceed entirely in the desired direction. A subsidiary reaction occurs by secondary condensation involving the simultaneous formation of a small amount of 1,4-di-d-neomenthyl-2,5-dioxypiperazine, as indicated by the equation



The extent of the subsidiary reaction is however very limited and does not appreciably effect the yield from the main reaction.

(b) The free menthylglycines, on pyrolysis, show an even greater tendency to undergo a similar secondary condensation, two molecules of water being eliminated between two molecules of glycine, as follows:-



In the case of d-neomenthylglycine, pyrolysis gives an 85% yield of N-methyl-d-neomenthylamine. Formation of piperazine is therefore definitely a subsidiary reaction in this instance, occurring to the extent of not more than 15%. The piperazine condensation is

however much more marked in the case of l-menthylglycine, where pyrolysis results in a 60% yield of N-methyl-l-menthylamine. This increase in the extent of the subsidiary reaction may well be due to the spatial effect of the neighbouring isopropyl group in the latter molecule. It is of interest to note at this stage that pyrolysis of N-phenylglycine under similar conditions gives a 70% yield of piperazine, this being therefore the main reaction in this case. An indication of the reasons for the relative variations in these two reactions on the basis of the electronic theory will be given later (p.28).

This method of N-alkylation has now been further applied to effect the conversion of mono-N-methylated menthylamines into the corresponding di-N-methylated bases. Continuing the progressive N-methylation of l-menthylamine, slightly more than two molecules of N-methyl-l-menthylamine were condensed with one molecule of ethyl chloroacetate for 6 hours on an oil bath at 140°. The hydrochloric acid formed was fixed by the excess base as before.

$$2C_{10}H_{19}\cdot NH\cdot CH_3 + Cl\cdot CH_2\cdot COOEt \longrightarrow C_{10}H_{19}\cdot N(CH_3)\cdot CH_2\cdot COOEt + C_{10}H_{19}\cdot NH\cdot CH_3,HCl$$

A quantity of 5% methyl alcoholic potassium hydroxide sufficient to hydrolyse the ethyl-N-methyl-l-menthylglycine and neutralise the hydrochloric acid was then added and the mixture refluxed for two hours on the waterbath.

$$C_{10}H_{19}\cdot N(CH_3)\cdot CH_2\cdot COOEt + C_{10}H_{19}\cdot NH\cdot CH_3,HCl + 2KOH \longrightarrow C_{10}H_{19}\cdot N(CH_3)\cdot CH_2\cdot COOK + C_{10}H_{19}\cdot NH\cdot CH_3 + EtOH + KCl + H_2O$$

The alcohol and excess N-methyl-l-menthylamine were then removed by steam-distillation and the base recovered as hydrochloride. The aqueous alkaline solution was concentrated, cooled in ice and saturated with carbon dioxide. No precipitate was obtained in this case, owing to the extreme solubility of N-methyl-l-menthylglycine. The solution was therefore just acidified with dilute hydrochloric acid and evaporated to dryness. The hydrochloride so obtained was extracted with chloroform and then converted into the insoluble calcium salt with calcium hydroxide solution. Treatment of the calcium salt with the calculated amount of sulphuric acid, removal of the insoluble calcium sulphate by filtration and evaporation of the resulting neutral solution to dryness yielded the required N-methyl-l-menthylglycine.

$$C_{10}H_{19}\cdot N(CH_3)\cdot CH_2\cdot COOK + 2HCl \longrightarrow C_{10}H_{19}\cdot N(CH_3)\cdot CH_2\cdot COOH,HCl + KCl$$

$$2C_{10}H_{19}\cdot N(CH_3)\cdot CH_2\cdot COOH,HCl + 2Ca(OH)_2 \longrightarrow (C_{10}H_{19}\cdot N(CH_3)\cdot CH_2\cdot COO)_2Ca + CaCl_2 + 4H_2O$$

$$(C_{10}H_{19}\cdot N(CH_3)\cdot CH_2\cdot COO)_2Ca + H_2SO_4 \longrightarrow 2C_{10}H_{19}\cdot N(CH_3)\cdot CH_2\cdot COOH + CaSO_4$$

The N-methyl-l-menthylglycine was recrystallised and heated for one hour on an oil bath at 200°. Decomposition occurred, yielding N-dimethyl-l-menthylamine and carbon dioxide.

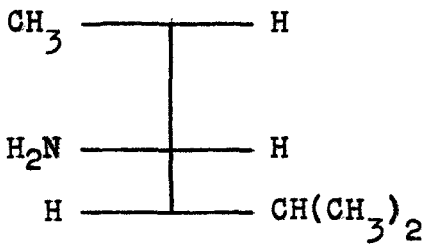
$$C_{10}H_{19}\cdot N(CH_3)\cdot CH_2\cdot COOH \longrightarrow C_{10}H_{19}\cdot N(CH_3)_2 + CO_2$$

The tertiary base was removed by steam-distillation from alkaline solution. After extraction with ether and drying, fractionation gave an almost quantitative yield of N-dimethyl-l-menthylamine.

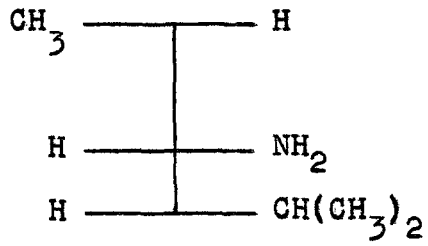
In a like manner the progressive N-methylation of d-neomenthylamine has been carried to the tertiary stage by condensation of N-methyl-d-neomenthylamine with ethyl chloroacetate and hydrolysis of the resulting ethyl-N-methyl-d-neomenthylglycine with alcoholic potassium hydroxide. The free N-methyl-d-neomenthylglycine

was again too soluble to be precipitated by saturating the aqueous alkaline solution of its potassium salt with carbon dioxide. Neutralisation with dilute hydrochloric acid and evaporation to dryness yielded a syrup which crystallised on cooling. The organic part was extracted with chloroform and found to consist of the required N-methyl-d-neomenthylglycine. Recrystallisation from ethyl acetate gave the pure product which adsorbed water-vapour from the atmosphere giving a stable dihydrate, $C_{10}H_{19}\cdot N(CH_3)\cdot CH_2\cdot COOH.2H_2O$.

On heating N-methyl-d-neomenthylglycine at 200° for one hour it melted and decomposed. In this instance, however, dimethylamine was evolved in addition to carbon dioxide. The yield of N-dimethyl-d-neomenthylamine was found to be slightly less than 60%, owing to the simultaneous formation of d-Δ^3-menthene, a result which must be attributed to the ready 3,4-trans-elimination (c.f. Read and Grubb, J.C.S. 1934, 1781) characteristic of the d-neomenthylamine and d-neomenthol series. Consideration of the relative molecular configurations of l-menthylamine and d-neomenthylamine (I and II) illustrates how trans-elimination only occurs in the latter series and explains why no menthene was observed in the decomposition of N-methyl-l-menthylglycine.



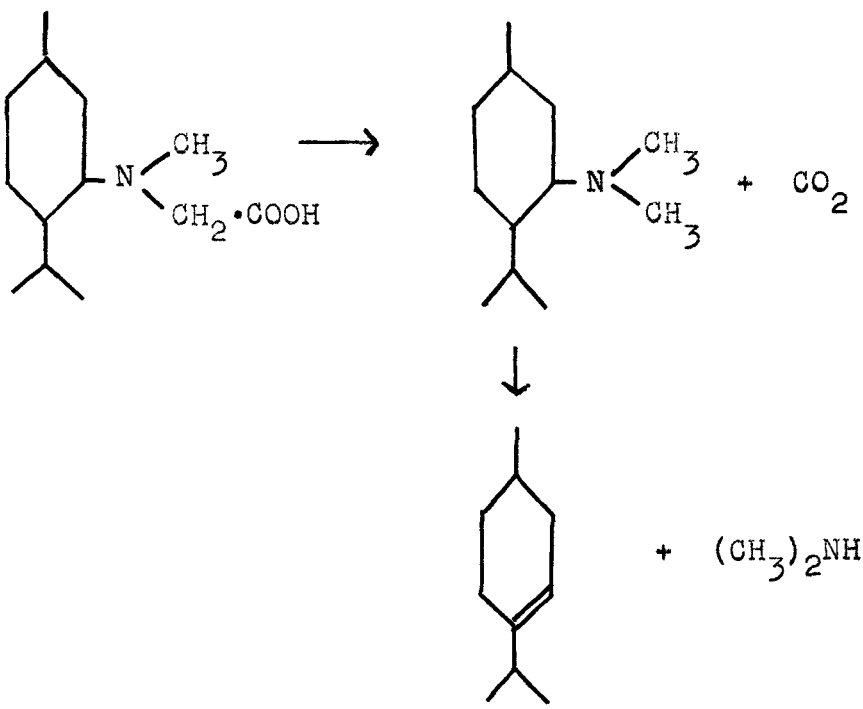
I. l-menthylamine.



II. d-neomenthylamine.

As regards the mechanism for the formation of menthene during the decomposition of N-methyl-d-neomenthylglycine, there would appear to be two alternatives, either:-

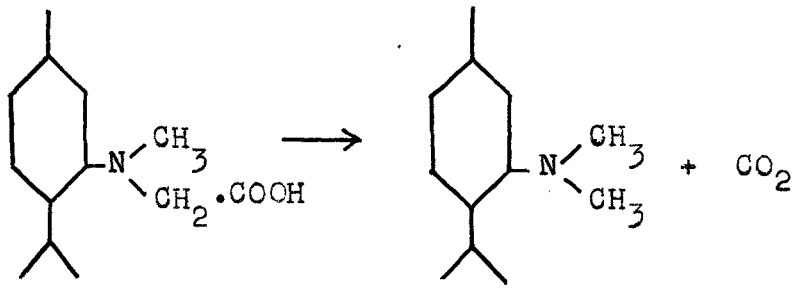
(1) Complete decomposition of the glycine compound giving N-dimethyl-d-neomenthylamine and carbon dioxide and then trans-elimination of dimethylamine from part of the N-dimethyl-d-neomenthylamine giving menthene at the temperature of the reaction.



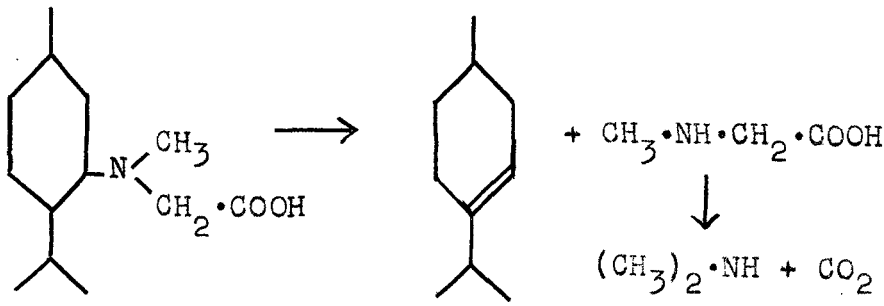
or:-

(2) A two-way decomposition, part of the N-methyl-d-neomenthylglycine decomposing normally to give carbon dioxide and N-dimethyl-d-neomenthylamine and part decomposing to give menthene and methyl glycine, which, at the temperature of the reaction decomposes spontaneously on formation yielding dimethylamine and carbon dioxide.

(a)



(b)



Although the final result is the same (2) would appear to be more probable, since, when a little pure N-dimethyl-d-neomenthylamine was distilled under ordinary pressure no dimethylamine was detected during the distillation and the distillate contained no menthene.

By means of this method of N-alkylation, therefore, a complete N-methylation of the two stereoisomeric primary bases, l-menthylamine and d-neomenthylamine has been achieved. The isolation and purification of the intermediate glycine compounds at each stage of the process may be claimed as a guarantee of the chemical and stereochemical purity of the derived secondary and tertiary bases. The physical constants of these bases have been determined and these constants are compared in tables I and II with those already measured by Read and Storey (J.C.S. 1930, 2761) for the corresponding primary bases. A summary of the yields obtained by this method is given by the following scheme:-

l-menthylamine	d-neomenthylamine
↓ 70%	↓ 84%
l-menthylglycine	d-neomenthylglycine
↓ 60%	↓ 85%
N-methyl-l-menthylamine	N-methyl-d-neomenthylamine
↓ 88%	↓ 90%
N-methyl-l-menthylglycine	N-methyl-d-neomenthylglycine
↓ 95%	↓ 60%
N-dimethyl-l-menthylamine	N-dimethyl-d-neomenthylamine

TABLE I.

Physical constants of l-menthylamine series.

Physical Constant	l-menthylamine	N-methyl-l-menthylamine	N-dimethyl-l-menthylamine
Boiling point	81-82°/12mm.	87°/12mm.	90-90·5°/10mm.
Density	0·8525/25°	0·8531/17°	0·8462/17°
Refractive index	1·4600/25°	1·4587/17°	1·4584/17°
α_D homog. (1dm.)	-37·97°/25°	-66·78°/17°	-51·18°/17°
$[\alpha]_D$ homog.	-44·53°/25°	-78·28°/17°	-60·48°/17°
$[\alpha]_D$ chloroform	-38·2°/25°	-69·17°/17°	-59·67°/17°

TABLE II.

Physical constants of d-neomenthylamine series.

Physical Constant	d-neomenthyl-amine	N-methyl-d-neomenthyl-amine	N-dimethyl-d-neomenthyl-amine
Boiling point	84°/13mm.	87°/12mm.	93°/12mm.
Density	0·8551/25°	0·8504/17°	0·8470/17°
Refractive index	1·4614/25°	1·4562/17°	1·4597/17°
α_D homog. (1dm.)	+12·93°/25°	+17·38°/17°	+36·16°/17°
$[\alpha]_D$ homog.	+15·12°/25°	+20·44°/17°	+42·69°/17°
$[\alpha]_D$ chloroform	+8·7°/25°	+26·4°/17°	+40·71°/17°

Application of the method to the piperitylamines.

Application of this method of N-alkylation to the N-methylation of the piperitylamines was expected to yield as satisfactory results as was the case in the menthylamine series. The results obtained were, however, extremely disappointing. In a preliminary experiment, two and a half molecular proportions of dl-piperitylamine were condensed with one molecular proportion of ethyl chloroacetate, the resulting ethyl-dl-piperitylglycine hydrolysed as before with 5% methyl alcoholic potassium hydroxide and an attempt made to precipitate the free dl-piperitylglycine by passing carbon dioxide into the aqueous alkaline solution in the same manner as described for the corresponding menthylglycines. In this case, however, no precipitation occurred, the glycine being apparently very soluble in water. It was endeavoured to isolate the dl-piperitylglycine by evaporating the solution to dryness and extracting with a suitable solvent. The potassium salt was however obtained. Acidification with dilute hydrochloric acid instead of carbon dioxide and evaporation to dryness yielded the hydrochloride, but it was found to be impossible to convert this compound back into the free glycine, since the corresponding calcium and barium salts were soluble in

water. The original method was therefore modified, two molecules of dl-piperitylamine being condensed with one molecule of ethyl chloroacetate in dry benzene.

$$2C_{10}H_{17}\cdot NH_2 + Cl\cdot CH_2\cdot COOEt \longrightarrow C_{10}H_{17}\cdot NH\cdot CH_2\cdot COOEt + C_{10}H_{17}\cdot NH_2,HCl$$

The dl-piperitylamine hydrochloride formed was removed by shaking with water and recovered from the aqueous solution. The ethyl-dl-piperitylglycine was itself isolated by fractionation of the dried benzene solution. It was found to yield a crystalline acid oxalate and was therefore purified by this means, the pure ester being reliberated from the oxalate with excess alkali. The pure ethyl-dl-piperitylglycine was then hydrolysed with a 5% methyl alcoholic potassium hydroxide solution, which had previously been titrated against standard hydrochloric acid using methyl orange as indicator.

$$C_{10}H_{17}\cdot NH\cdot CH_2\cdot COOEt + KOH \longrightarrow C_{10}H_{17}\cdot NH\cdot CH_2\cdot COOK + EtOH$$

The alkaline solution was then treated with the calculated quantity of standard hydrochloric acid required to neutralise the alkali used and the whole evaporated to dryness. dl-Piperitylglycine was separated

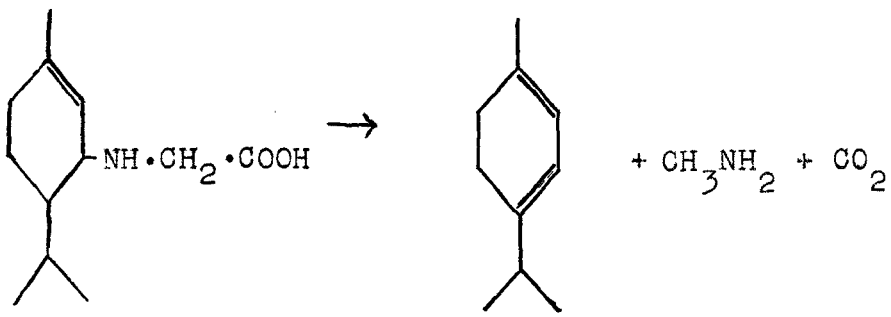
from the inorganic residue by extraction with chloroform.

$$C_{10}H_{17}\cdot NH\cdot CH_2\cdot COOK + HCl \longrightarrow C_{10}H_{17}\cdot NH\cdot CH_2\cdot COOH + KCl$$

The substance was purified by recrystallisation from water, in which it was very soluble, and was found to give satisfactory figures on analysis.

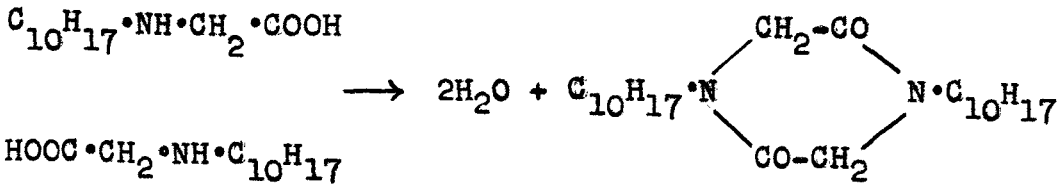
dl-Piperitylglycine, on pyrolysis, was found to undergo a three-way decomposition yielding

(1) A terpene fraction, consisting essentially of α-terpinene;



dl-piperitylglycine α-terpinene

(2) An appreciable amount of 1,4-di-dl-piperityl-2,5-dioxypiperazine by elimination of two molecules of water between two molecules of glycine;



(3) A small amount of N-methyl-dl-piperitylamine by elimination of carbon dioxide.

$$C_{10}H_{17}\cdot NH\cdot CH_2\cdot COOH \longrightarrow C_{10}H_{17}\cdot NH\cdot CH_3 + CO_2$$

Of these reactions, the desired reaction (3) was subsidiary in extent to the others. The yield of secondary base was extremely small, although sufficient to allow of its characterisation as nitrosamine. Hence, from this preliminary experiment, it would appear that the presence of the 1,2 double bond in piperitylamine renders the method of N-alkylation so successfully applied to the menthylamines of little or no value in the case of the piperitylamines.

In spite of the difficulties outlined above d-piperitylamine and l-piperitylamine have been converted into N-methyl-d-piperitylamine and N-methyl-l-piperitylamine respectively by this method. Starting from a specimen of d-piperitylamine having α_D +43·5° (1dm. homog.), a specimen of N-methyl-d-piperitylamine hydrochloride was prepared having $[\alpha]_D$ +96·5° (c. 2·0, H_2O). The l-piperitylamine used had α_D -61·5° (1dm. homog.) and the derived N-methyl-l-piperitylamine hydrochloride $[\alpha]_D$ -96·7° (c. 1·982, H_2O). Since the starting materials were impure in both cases, but of differing degrees of impurity, the close similarity in the two values +96·5° and -96·7°

obtained for the rotatory power of N-methyl-d-piperitylamine and N-methyl-l-piperitylamine hydrochloride, respectively, might well be advanced as a further claim for the efficacy of this process of N-methylation as far as stereochemical purification of intermediates is concerned. It might even be that these two hydrochlorides are stereochemically pure. An attempt was made to confirm this by mono-methylation of pure l-piperitylamine [α_D -81·38° (ldm. homog.)], using methyl iodide and sodium. The secondary base was extracted as N-methyl-l-piperitylnitrosamine, which was found however to decompose when hydrolysed by the method of Ladenburg (Ber. 12. 949 [1879]) yielding a tarry material from which no secondary base could be obtained.

Owing to the small yields of secondary base obtained in the first stage of the methylation, the planned continuance of the method through to the corresponding tertiary bases, as described for the menthylamines, above, had to be abandoned.

Application of the method to aniline.

N-Phenylglycine was prepared from aniline and ethyl chloroacetate by the general method described above. The amino-acid was not precipitated by passing carbon

dioxide into the solution of its potassium salt, but was brought down by careful addition of dilute hydrochloric acid. After purification, the N-phenylglycine was subjected to pyrolysis at 200°. On cooling and steam-distilling from alkaline solution a few drops of monomethylaniline were obtained. The main product, however, consisted of 1,4-diphenyl-2,5-dioxypiperazine, formed by condensation of two molecules of phenylglycine with elimination of two molecules of water. Here again, therefore, elimination of carbon dioxide is the subsidiary reaction, the main reaction being the piperazine condensation.

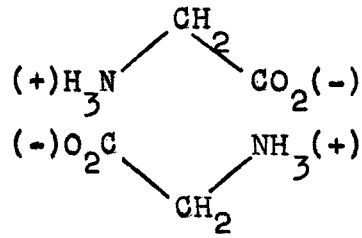
Since monomethylaniline is readily available, methylation of N-methylaniline to N-dimethylaniline by this method was attempted. Condensation of monomethylaniline with ethyl chloroacetate, hydrolysis of the resulting ethyl-N-methyl-phenylglycine and careful addition of hydrochloric acid to the resulting alkaline solution yielded N-methyl-phenylglycine as a viscous liquid. This was found to decompose easily on heating, splitting off carbon dioxide with the formation of N-dimethylaniline.

The mechanism of the two-way decomposition of mono-substituted glycines on pyrolysis.

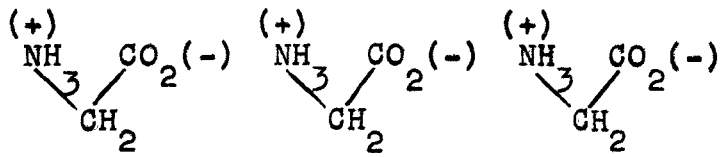
It has been shown how d-neomenthylglycine and l-menthylglycine undergo two-way decomposition on pyrolysis. The main reaction involves the splitting off of carbon dioxide and the formation of the corresponding secondary base, while a subsidiary reaction also occurs, two molecules of water being eliminated between two molecules of glycine giving rise to dioxypiperazines. Further, in the case of N-phenylglycine, the latter reaction becomes the main reaction and the yield of piperazine is of the order of 70%, whereas decomposition with elimination of carbon dioxide occurs to only a small extent. Thirdly, in the case of the piperitylglycines, the extent of the piperazine condensation is intermediate between the two, being greater than with the menthylglycines but less than is the case with phenylglycine. It can therefore be stated that the extent of the dioxypiperazine condensation increases with increasing electronegative nature of the radical attached to the secondary imino-group. The reason for this is revealed by considering the problem in the light of the electronic theory.

The amino-acids, $H_2N \cdot R \cdot COOH$, contain both an acidic and a basic group and salt formation can occur

between them, giving rise to inner salts or zwitterions of the type $H_3\overset{+}{N}\cdot R\cdot COO(-)$. We are here concerned with amino-acids in the solid, or, at the most, liquid state. The fact that this view of the constitution of the molecule of an aliphatic amino-acid holds for the crystalline state is revealed by an examination of crystal structure. The crystals have a density greater than that of the majority of organic compounds and this shows that the packing is ionic, consisting of such zwitterions held together by electrostatic forces. Glycine itself, for instance occurs in two crystalline forms, one of these being built up of double molecules arranged positive charge to negative charge



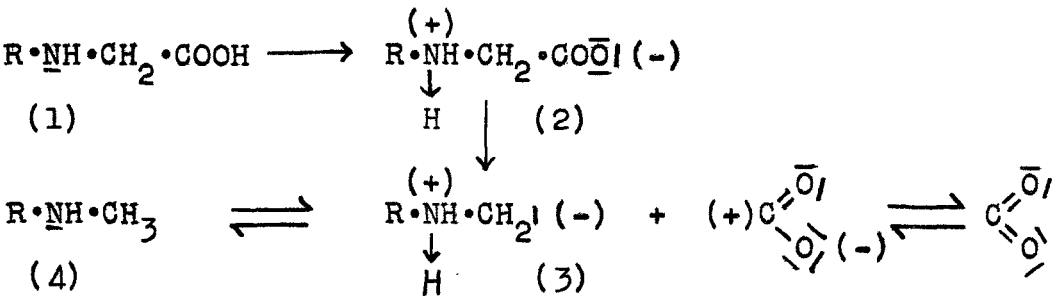
and the other of long chains of molecules arranged in the same way.



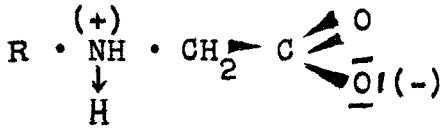
This packing will also be found in substituted glycines of the type $R\cdot NH\cdot CH_2\cdot COOH$, but the extent of the

zwitterion formation will of course be influenced by the nature of the substituting atom or group. For instance, if R is an aliphatic radical, such as methyl, the tendency to inner salt formation will be greater than in cases where the substituting radical is aromatic in nature, since the aliphatic amines have greater dissociation constants and greater basicity than the corresponding aromatic compounds. Hence, phenylglycine will show less tendency for zwitterion formation than methylglycine, while hydroaromatic substituents will more closely resemble the aliphatic type. Thus the menthylglycines will be more closely allied to the aliphatic glycines than to, say, phenylglycine, and will show a considerable tendency to zwitterion formation.

The elimination of carbon dioxide observed when substituted glycines are subjected to pyrolysis must be formulated from the zwitterion formula as indicated by the scheme below, where the dash represents a lone electron pair.



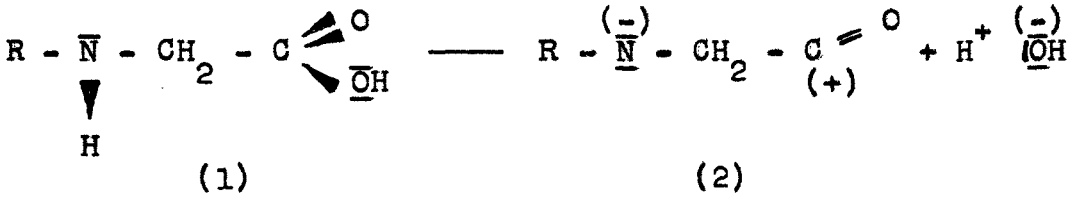
At the moment of decomposition, the hydrogen previously attached to the carboxyl group is firmly attached to the nitrogen by a valency bond. When the temperature is sufficiently high to completely break the already inherently unstable C-C linkage, an ammonium carbeniate form (3) is formed. Proton movement and readjustment of valencies then occur with formation of the tautomeric secondary base (4). The fact that the bond between the α carbon atom and the carbon atom of the carboxyl group is inherently unstable may be illustrated by drawing the zwitterion (2) in the diagrammatic form shown below. The oxygen atoms of the carboxyl group, having greater electron affinities, act as key atoms (Schlüsselatome), inducing inequality of sharing in the neighbouring bond. This inequality is illustrated by bonds thickened towards the end to which the common electron pair is mostly attracted.



In the limiting state, when decomposition occurs, this bond will therefore break as shown above giving $-CH_2^{\ddagger}(-)$ and $(+)C\equiv$. Hence, if this representation of the reaction be correct, the greater the tendency to inner salt formation, the greater will be

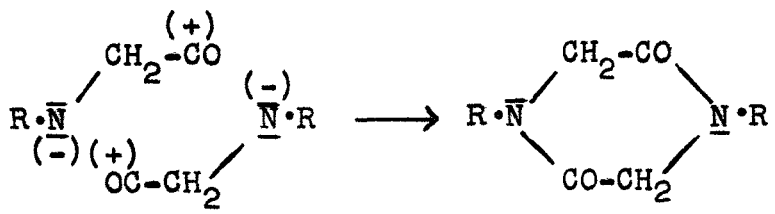
the tendency for decomposition into secondary base and carbon dioxide.

For dioxypiperazine condensation, however, water must be eliminated, in other words, hydrogen comes off as a proton and the hydroxyl radical as an anion. This must be formulated from the amino-acid in its ordinary form as shown below.



(1) (2)

Here we have key atoms nitrogen and oxygen. The hydrogen of the imino-group comes off as a proton, leaving a second lone electron pair on the nitrogen, which then assumes a negative charge. The hydroxyl group takes the electron pair of the ≡C-OH bond with it, leaving an electron gap (Elektronenlücke) or, in other words, a positive charge. The resulting carbenium form (2) will combine with its like to form dioxypiperazine.



Hence, the less the tendency to inner salt formation, the greater will be the tendency to dioxypiperazine condensation.

Summing up, we see that, when the substituent R is electronegative in character, as, for instance, is the case in phenylglycine, dioxypiperazine condensation will be the main reaction, since the electronegative phenyl radical reduces the basicity of the nitrogen and opposes inner salt formation. Aliphatic substituents, however, - and to this class must be reckoned the menthylglycines - give rise to much stronger bases and increase the tendency to zwitterion formation. Hence in such cases, decomposition into secondary base is the main reaction. The piperitylglycines, having a 1,2 double bond in the substituent group, will form an intermediate case and the dioxypiperazine formation will be more marked than in the case of the menthylglycines.

The behaviour of l-menthyl- and d-neomenthyl-trimethyl-ammonium iodides and hydroxides on dry distillation.

l-Menthyl- and d-neomenthyl-trimethylammonium iodides were prepared by a slight modification of the method of Wallach (Annalen. 276, 301, [1893]). An examination of their behaviour on dry distillation yielded interesting results. The dry distillation of l-menthyl-trimethylammonium iodide under ordinary atmospheric pressure gave a 30% yield of menthene and trimethylamine hydriodide, the menthene having a moderately high rotatory power of α_D +75·24° (1dm. homog.), together with a 70% yield of N-dimethyl-l-menthylamine, identical in every respect with the tertiary base obtained from the methylation of l-menthylamine by the new method of N-alkylation. Dry distillation of d-neomenthyl-trimethyl-ammonium iodide, on the other hand, gave a quantitative yield of menthene and trimethylamine hydriodide. The rotatory power of the menthene was of the same magnitude as above, namely α_D +80·6°. Similarly, dry distillation of l-menthyl-trimethylammonium hydroxide gave a 30% yield of menthene, trimethylamine and water and a 70% yield of N-dimethyl-l-menthylamine, whereas dry distillation of d-neomenthyl-trimethylammonium hydroxide gave a quantitative yield of menthene, trimethylamine and water.

Wallach (Annalen. 300, 285, [1898]), who first prepared these quaternary hydroxides stated wrongly that they both decomposed in the same way to form water, trimethylamine and menthene. The fact is, however, that only the d-neo- compound decomposes in this way, while l-menthyl-trimethylammonium hydroxide undergoes a two-way decomposition yielding only 30% menthene. These results are of great interest since, in the former case, trans-elimination is involved and in the latter cis-elimination, so that here again we have confirmation of the configurations assigned to d-neomenthylamine and l-menthylamine respectively. Further, the d-Δ^3-menthene obtained in quantitative yield from the decomposition of d-neomenthyl-trimethylammonium hydroxide had the high rotatory power $[\alpha]_D^{20^\circ}$ +112·9° (homog.). d-Δ^3-Menthene of such stereochemical purity had previously only been obtainable by the laborious Xanthogene-ester method of Tschugaeff (Ber. 32, 3333 [;899]); compare also Read and Robertson (J.C.S. 1926, 2217). Here, however, we have a method of preparing it more conveniently and in better yield, starting from commercial menthone, by the route:-

Menthone (commercial) $\longrightarrow$ formyl-d-neomenthylamine $\xrightarrow{83\%}$ d-neomenthyl-trimethylammonium iodide $\xrightarrow{100\%}$ d-neomenthyl-trimethylammonium hydroxide $\xrightarrow{95\%}$ d-Δ^3-menthene.

The menthene obtained from l-menthyl-trimethylammonium hydroxide by dry distillation had the amazingly high rotatory power $[\alpha]_D^{17^\circ}$ +131·7° (homog.). This is by far the highest value yet measured for any menthene, but it is possible, however, that this is not d-Δ^3-menthene but rather d-Δ^2-menthene.

The effect of progressive N-methylation on ionic rotatory power.

From the values obtained in the course of these experiments for the rotatory powers of the salts of the methylated menthylamines, including the quaternary compounds, the molecular rotatory powers $[M]_D$ have been calculated for the l-menthylamine series and the d-neomenthylamine series respectively. The resulting values are given in table III. It will be seen that, in both series, progressive N-methylation lends an increasing laevo-rotatory tendency to the asymmetric cation.

TABLE III.

The Molecular rotation of the N-methylated menthylamines.

Salt of base	l-menthylamine series	d-neomenthylamine series
$[R \cdot NH_3]Cl$	- 70·1°	+41·2°
$[R \cdot NMeH_2]Cl$	-108·4°	+34·3°
$[R \cdot NMe_2H]Cl$	-110·0°	+33·6°
$[R \cdot NMe_3]I$	-127·6°	-63·4°

Read and Robertson. J.C.S. 1926, 2217.

Reduction of the hydrated azine of dl-piperitone.

The conditions under which a maximum yield of dl-piperitylamine was obtained have been described in the practical section. Several experiments were however performed before this result was achieved. It might be of value to outline these briefly here.

Reduction of the hydrated azine of l-piperitone, a considerable quantity of which had been left by Walker (1933) and which had therefore stood for at least seven years, gave a maximum yield of 50% of that obtained by him, i.e. from 70g. of the hydrated azine only 15-20g. of dl-piperitylamine were obtained. It was also confirmed in this series of experiments that pure zinc powder must be used if a satisfactory reduction is to be realised. Unusually large amounts of neutral oil containing menthone and isomenthone were formed during the reductions. Since this can only have been formed by hydrolysis followed by reduction, it would appear that this specimen of hydrated azine contained more water than a freshly prepared specimen. The freshly prepared compound was brownish-red in colour, whereas the sample used in the reduction had become light-red in colour. There would appear to be two possible explanations for this change in colour. The substance may have adsorbed water slowly with the reproduction of some of the original dihydrated azine,

the yellow colour of which would lighten the colour of the liquid as a whole. Or, alternatively, the hydrated azine might have split out the remaining molecule of water with the production of the true azine which would be redder in colour. Of these, the former alone would account for the large yield of neutral oil by hydrolysis and reduction, since the water of the monohydrated azine is removed in any case when it is treated with glacial acetic acid yielding the true azine which dissolves in its lactam form. Further it is this one molecule of water which is responsible for the smaller amount of neutral oil formed along with the required dl-piperitylamine in normal reductions.

In preparing fresh samples of the hydrated azine, dl-piperitone was used, since asymmetry is completely annulled in any case during the reduction process. The ether solution of the fully hydrated azine was dried for two to three days over anhydrous calcium chloride and the substance used immediately after removal of the ether. Further, since hydrolysis occurs during the process of reduction, it was considered inadvisable to allow the reduction to proceed so slowly for two hours in the cold before raising the temperature, since the hydrolysis may occur largely at this stage. The reduction was accordingly speeded up by raising the temperature to about

40-50° at the beginning. However, the maximum yield obtained in this way was no better than the yields achieved by Walker (Dissertation. St. Andrews, 1933).

The optical resolution of dl-piperitylamine.

Walker (Dissertation. p.18) mentioned a curious feature observed on one or two occasions in the resolution of dl-piperitylamine. It was sometimes found impossible to crystallise the l-piperitylamine hydrogen d-tartrate to maximum optical rotation (hanging resolution). Walker stated that this anomaly was only observed with specimens of dl-piperitylamine which had been kept for some time before application of the tartaric acid. This rather mystical result has however been borne out by the present work. In every case the base used was freshly prepared and no hanging resolution occurred. Further, by dissolving the base immediately after distillation in methylated spirits and subsequent treatment with d-tartaric acid, a hydrogen d-tartrate was obtained having $[\alpha]_D$ -47·8° (c. 1·4, H_2O) compared with the value -43° given by Walker. The l-piperitylamine liberated from this salt had α_D -81·38° (1dm. homog.) compared with the previous value of -75·94°.

C. EXPERIMENTAL.

1. Methylation of d-neomenthylamine.

[A]. N-Methyl-d-neomenthylamine.

(a) Formyl-d-neomenthylamine.

(c.f. J.C.S. 1926, 2219).

In a 1000cc. Claisen Flask were placed 228g. ammonium formate and 190g. l-menthone. The flask was fitted with a cork carrying a thermometer reaching almost to the bottom and the side-limb of the flask was connected to a small condenser set for distillation. The contents of the flask were heated with a small flame. The mixture melted to two layers and distillation began. At 165°, the mixture became homogeneous and the reaction took place with moderate foaming. During this process, water, menthone and ammonium carbonate (solid) distilled over (140-165°). The heating was continued until the temperature reached 200°, which was after about 3 hours. At 200°, the heating was stopped, the upper layer of menthone separated from the distillate and returned to the flask without drying. Heating was then continued at 200° for a further 3 hours. When the mixture was cold it was extracted with chloroform, washed three times with water to remove ammonium formate and dried

over anhydrous sodium sulphate. The chloroform was then distilled off and the residue fractionated to remove unchanged menthone (up to 150cc. at 15mm.). The residue was then cooled, treated with approximately its own volume of ether and allowed to stand. Crystals began to form almost immediately. After a time, these were filtered off and washed with a little ether. Yield: 58g. m.p. 117-18°. After recrystallisation from ether the crystals had

$[\alpha]_D$ + 53·8° (c. 1·76, $CHCl_3$).
+ 62·4° (c. 1·53, abs. alcohol).

(b) Hydrolysis of formyl-d-neomenthylamine.

(c.f. J.C.S. 1926, 2219, also Annalen 276, 308, [1893]).

A mixture of 90g. formyl-d-neomenthylamine and 250cc. concentrated hydrochloric acid was boiled in a litre-round-bottom flask under a reflux condenser until it was found that a test-sample did not develop a turbidity when diluted with water. The hydrolysis was complete in about four hours. The solution was then cooled, diluted with 250cc. water and transferred to a 2-litre flask. A solution of 300g. sodium hydroxide in 300cc. of water was slowly added. The reaction mixture was strongly cooled during the addition of the

alkali. When all the acid had been neutralised the liberated amine was purified by distillation in steam. The distillate was rendered slightly acid by the addition of dilute hydrochloric acid and was then evaporated to dryness. The weight of the hydrochloride obtained was 88g. (93·4% theory) - colourless needles, which had m.p. 189° and $[\alpha]_D$ + 18·3° (c. 2·0000, H_2O). Recrystallisation from a little water gave pure d-neomenthylamine hydrochloride, having m.p. 189° and $[\alpha]_D$ + 21·5° (c. 1·44, H_2O).

(c) d-neo-Menthylglycine.

(i) Ethyl-d-neomenthylglycine.

To 120g. (2·5 mols.) d-neomenthylamine hydrochloride in aqueous solution in a conical flask was added sufficient 2N. caustic soda to liberate the base, which was extracted with ether. The ether solution was washed twice with water, dried over anhydrous sodium sulphate and the ether then evaporated off under diminished pressure in a litre-round-bottom flask. To the free d-neomenthylamine so obtained were added 30g. (1 mol.) of ethyl chloroacetate. The flask was fitted with a reflux condenser, closed with a soda lime tube. The mixture was heated on an oil-bath at 130° for four hours.

(ii) Hydrolysis of ethyl-d-neomenthylglycine.

When reaction (i) was complete, the contents were transferred to a 2-litre flask, 750cc. of a 5% methyl alcoholic solution of potassium hydroxide added and the mixture refluxed gently for two hours.

(iii) Isolation of d-neomenthylglycine and dioxypiperazine derivative.

The solution was then subjected to steam distillation to remove the alcohol and excess d-neomenthylamine. The amine was recovered as hydrochloride (70g.). On allowing the residue after the steam distillation to cool, a small white precipitate gradually came down. This was extracted with ether. The aqueous solution was evaporated to 250cc. on the waterbath, cooled in ice and carbon dioxide passed through till acid, when a creamy-white precipitate of the required d-neomenthylglycine came down. This was filtered off, washed with a little ice-cold water and dried on a porous plate. From the mother-liquor a further crop of crystals was obtained. Total yield was 44g. (84·4% theory, calculated from weight of $Cl\text{-}CH_2\text{-}COOEt$ used) of colourless prisms, which on recrystallisation from a little water had m.p. 182° and $[\alpha]_D$ + 32·2° (c. 2·3, alcohol) and $[\alpha]_D$ + 28·1 (c. 1·3855, H_2O).

Analysis:

Found:-	C.	67·2%,	H.	10·9%
$C_{12}H_{23}O_2N$ requires:-	C.	67·6%,	H.	10·8%.

The etherial solution was washed with water and on addition of dilute hydrochloric acid to the ether solution, a white precipitate came down. This was filtered off, washed with ether, then with water. Weight: 2g. Recrystallisation from aqueous methyl alcohol gave colourless prisms, m.p. 242° under decomposition and $[\alpha]_D$ + 42·9° (c. 2·0275, $CHCl_3$). The substance was suspected to be the hydrochloride of 1,4-di-d-neomenthyl-2,5-dioxypiperazine, probably formed during stage (ii) above. The hydrochloride did not appear to be a very definite one. Analysis gave N. 7·2%, Cl. 8·6%. The monohydrochloride of the compound, $C_{24}H_{42}O_2N_2$, has N. 6·6%, Cl. 8·3%. Accordingly, the free base was prepared by shaking some of the hydrochloride with 2N. sodium hydroxide in a separating funnel and extracting with ether. The etherial solution was washed with sodium hydroxide, then with water and dried over anhydrous sodium sulphate. On evaporating off the ether, the residue solidified. The free base was recrystallised from aqueous methyl alcohol and had m.p. 63° and $[\alpha]_D$ + 43·9° (c. 2·1090, $CHCl_3$).

Analysis:

Found:- C. 72·1%, H. 11·7%, N. 7·8%, O. 8·4%.

$C_{24}H_{42}O_2N_2$ requires:- C. 73·8%, H. 10·8%, N. 7·2%, O. 8·2%.

The analysis figures indicate that the substance is not quite pure, but the ratio of N:O of 1:1 shows that the substance is of the type indicated. Further purification was not attempted, as the substance is only of interest as far as its formation influences the yield of the main reaction. Isolation of the same substance in the next stage of the process proved that the suggested formula is the correct one (see below).

(d) N-Methyl-d-neomenthylamine hydrochloride.

40g. of d-neomenthylglycine heated on an oil-bath at 210° under an air condenser melted with effervescence. The formation of water-vapour was also noticed. The heating was maintained for one hour. Then 10cc. of 2N. sodium hydroxide solution were added and the product was distilled in steam. A colourless refractive oil rapidly passed over with the steam. The amine was isolated as the hydrochloride (33g. - 85·5% theory) which was recrystallised from a little water. The hydrochloride was strongly efflorescent. After drying in a vacuum desiccator, the hydrochloride had m.p. 195-6° and $[\alpha]_D$ + 16·7° (c. 2·0, H_2O).

Analysis:

Found:- Cl. 17·7%.

$C_{11}H_{24}NCl$ requires:- Cl. 17·8%.

The presence of water-vapour above led to the belief that a condensation reaction had again occured giving rise to 1,4-di-d-neomenthyl-2,5-dioxypiperazine. Accordingly, the residue after the steam distillation was not discarded and it was found possible to isolate from it, in the same manner as before, the compound previously obtained. Thus, we may conclude that when d-neomenthylglycine is heated above its m.p. two reactions occur, namely,

(a) Elimination of carbon dioxide, resulting in the formation of N-methyl-d-neomenthylamine, and this is the main reaction, giving an 85% yield.

(b) A subsidiary reaction, the condensation of 2 molecules of d-neomenthylglycine with the elimination of 2 molecules of water, giving rise to a dioxypiperazine derivative.

c.f. Decomposition of phenylglycine under similar conditions gives a 70% yield of piperazine. (Bischoff, Hausdörfer, B. 25, 2271). In this case, the formation of 1,4-diphenyl-2,5-dioxypiperazine is the main reaction.

(e) N-Methyl-d-neomenthylamine.

50g. of N-methyl-d-neomenthylamine hydrochloride were dissolved in water and the base liberated with 2N. sodium hydroxide solution. This was extracted with ether, the ether solution washed with water and dried over anhydrous sodium sulphate. The ether was distilled off under diminished pressure and the residue fractionated. Pure N-methyl-d-neomenthylamine came over at 87°/12mm. Weight: 40g. N-methyl-d-neomenthylamine appears to be stable to carbon dioxide.

Physical Constants of N-methyl-d-neomenthylamine.

B.p.	87°/12mm.	
$D_4^{17°}$	0·8504	
$n_D^{17°}$	1·4562	
$\alpha_D^{17°}$	+17·38° (1dm. homog.)	
$[\alpha]_D^{17°}$	+20·44°	
$[\alpha]_D^{17°}$	+26·4° (c. 2·1100, $CHCl_3$)	
$[R_L]_D$	Found:-	54·03
	Calculated:-	54·63

Derivatives.

(i) Benzoyl-N-methyl-d-neomenthylamine.

To a solution of 2·0g. of N-methyl-d-neomenthylamine in 5cc. of freshly distilled pyridine were added 2·0g. of benzoyl chloride. The solution was left at room temperature for two days and was then poured into 50cc. of 2N. hydrochloric acid. The red syrup which separated was extracted with ether. The ether extract was washed once with dilute sulphuric acid and repeatedly with dilute sodium hydroxide solution until the red colour was removed from the solution. It was finally washed with water, dried and fractionated. A yellow syrup (3g.) was obtained. After a week at room temperature the syrup crystallised spontaneously. It was recrystallised from aqueous methyl alcohol at 0° and had m.p. 67° and $[\alpha]_D$ + 5·7° (c. 2·0, $CHCl_3$).

Analysis:

Found:-	C.	78·5%,	H.	9·6%.
$C_{18}H_{27}ON$ requires:-	C.	79·1%,	H.	9·9%.

(ii) p-Toluenesulphonyl-N-methyl-d-neomenthylamine.

Prepared as above. Obtained in the form of colourless needles from aqueous alcohol at 0°. Had m.p. 49° and $[\alpha]_D$ + 18·5° (c. 2·0, $CHCl_3$).

Analysis:

Found:-	C.	67·2%,	H.	9·0%.
$C_{18}H_{29}O_2NS$ requires:-	C.	66·9%,	H.	9·0%.

(iii) N-methyl-d-neomenthylnitrosamine.

5g. of N-methyl-d-neomenthylamine hydrochloride were dissolved in 25cc. of 2N. hydrochloric acid and a solution of 2·5g. sodium nitrite in 10cc. water added. The product was a light-brown oil which crystallised at room temperature. The nitrosoderivative was filtered off, washed with water and dried. Weight: 2·7g. Recrystallisation from aqueous alcohol gave pale yellow prisms, m.p. 62° and $[\alpha]_D$ + 19·9° (c. 2·1225, $CHCl_3$).

Analysis:

Found:-	C.	66·3%,	H.	10·9%.
$C_{11}H_{22}ON_2$ requires:-	C.	66·6%,	H.	11·1%.

[B]. N-di-Methyl-d-neomenthylamine.

(a) N-Methyl-d-neomenthylglycine.

(i) Ethyl-N-methyl-d-neomenthylglycine.

130g. (2·5 mols.) N-methyl-d-neomenthylamine hydrochloride were converted into the free base and condensed with 30g. (1 mol.) of ethyl chloroacetate in a litre-round-bottom flask, fitted with a reflux condenser. The temperature of the oil bath was taken up to the point where moderate refluxing occurred (140-150°). A white cake of the hydrochloride gradually formed. Heating was continued for six hours at 140-150°.

(ii) Hydrolysis of ethyl-N-methyl-d-neomenthylglycine.

When reaction (i) was completed, 750cc. of 5% methyl alcoholic potassium hydroxide were added, the mixture transferred to a 2-litre flask and boiled gently on a waterbath for two hours.

(iii) Isolation of N-methyl-d-neomenthylglycine.

The alcohol and excess N-methyl-d-neomenthylamine were steam-distilled away from the product and recovered as hydrochloride (78g.). The aqueous solution in the flask was concentrated to 250cc., cooled in ice and carbon dioxide passed through. No precipitate

of N-methyl-d-neomenthylglycine formed. This compound must therefore be much more soluble in water than the corresponding d-neomenthylglycine. The solution was just acidified with dilute hydrochloric acid and evaporated down. The liquid was found to become alkaline again after a short time. A further few drops of dilute hydrochloric acid were added until the solution was just acid to litmus and the solution then taken to dryness. The product was a syrup which crystallised on cooling. The N-methyl-d-neomenthylglycine was separated from the inorganic part of the residue by extraction with cold, absolute alcohol. On filtering and evaporating off the alcohol a syrup was obtained, which solidified on cooling. Ignition still gave a slightly alkaline residue. The alkaline portion was found to be quite insoluble in acetone. The product was accordingly extracted with cold acetone, filtered and the acetone evaporated off. The product solidified on cooling. Weight of N-methyl-d-neomenthylglycine obtained - 50·1g. (90% theory, calculated from the weight of ethyl chloroacetate used). Lassaigne's Test gave N and the substance gave no residue on ignition. Recrystallisation from ethyl acetate gave small white needles, m.p. 98°, which were slightly hygroscopic, adsorbing moisture from the air to form the stable dihydrate, which had

m.p. 55° and $[\alpha]_D$ +28·5° (c. 2·0, H_2O).

Analysis:- 4·568mg. dried at 40° in vacuo lost 0·621mg.

Found:- H_2O. 13·6%.

$C_{13}H_{25}O_2N.2H_2O$ requires:- H_2O. 13·7%.

Dried material gave:- C. 68·6%, H. 10·9%.

$C_{13}H_{25}O_2N$ requires:- C. 68·7%, H. 11·0%.

(b) Decomposition of N-methyl-d-neomenthylglycine. Formation of menthene and N-dimethyl-d-neomenthylamine.

20g. of pure N-methyl-d-neomenthylglycine were heated for one hour on an oil bath at 200° in a round-bottom flask fitted with an air condenser. Carbon dioxide was evolved and also a gas with a strong ammoniacal odour, which turned red litmus strongly blue. On cooling, the contents were treated with dilute hydrochloric acid to dissolve the base formed and a colourless oily layer of menthene separated out. This was extracted with ether, the ether solution washed with dilute hydrochloric acid, then thoroughly with water and dried over anhydrous sodium sulphate. After evaporating off the ether under diminished pressure, the menthene was fractionated. Pure liquid came over at 70°/15mm.

Weight of menthene obtained: 3·9g. (37·1% theory).
The menthene had $n_D^{16°}$ 1·4530, $\alpha_D^{16°}$ + 83·16° (1dm. homog.), $D_4^{16°}$ 0·8139 and $[\alpha]_D^{16°}$ + 102·2°.

Analysis:

Found:-	C.	H.
	85·94%	13·04%
	85·88%	13·05%
	86·22%	12·88%
$C_{10}H_{18}$ requires:-	86·96%	13·04%

The hydrochloric acid extract was made alkaline with 2N. sodium hydroxide solution, when a colourless refractive oil came out. This was extracted with ether, the ether solution washed with water and dried over anhydrous sodium sulphate. The ether was evaporated off under diminished pressure and the residue fractionated. Pure N-dimethyl-d-neomenthylamine came over at 93°/12mm. Yield: 8·1g. (58·2% theory).

(c) Characterisation of N-dimethyl-d-neomenthylamine.

(i) Formation of chloroplatinate.

0·6cc. of base was dissolbed in a minimum of dilute hydrochloric acid and a solution of 0·5g. platinic chloride in dilute hydrochloric acid added. An orange-

yellow precipitate formed immediately. This was filtered, washed thoroughly with water, then with absolute alcohol and dried in a desiccator. It had m.p. 196°.

Ignition gave:- Pt. 25·24%.

$[C_{10}H_{19}N(CH_3)_2\text{-}H]_2PtCl_6$ requires:- Pt. 25·14%.

(ii) Preparation of quaternary iodide.

To 2cc. base dissolved in 5cc. methyl alcohol were added 2cc. of methyl iodide and the mixture gently refluxed for one hour. The alcohol and excess methyl iodide were evaporated off under diminished pressure. The quaternary iodide solidified in the flask. Recrystallisation from a little acetone gave colourless prisms, m.p. 160·5° and $[\alpha]_D$ -19·5° (c. 2·0, H_2O).

(iii) Physical Constants of base.

B.p.	93°/12mm.
$\alpha_D^{17°}$	+36·16° (1dm. homog.)
$n_D^{17°}$	1·4597
$D_4^{17°}$	0·8470
$[\alpha]_D^{17°}$	+42·69°

$[\alpha]_D^{17^\circ}$ $+40\cdot71^\circ$ (c. 2·0270, $CHCl_3$).

$[R_L]_D$ Found:- 59·11

Calculated:- 59·34

(iv) Rotatory power of N-dimethyl-d-neomenthylamine hydrochloride.

To a weighed amount of pure N-dimethyl-d-neomenthylamine in a 20cc. polarimeter flask were added a few cc. of distilled water and the calculated quantity of standard hydrochloric acid solution added from a micro-burette. The flask was warmed gently on the waterbath, till the contents were homogeneous. The flask was then allowed to cool to room temperature, made up to the mark with distilled water and the rotatory power measured in a 2dm. tube.

Results:- Wt. of base in 20cc. polarimeter flask

= 0·3345g.

Amount of hydrochloric acid required

= 1·83cc. N HCl.

Wt. of hydrochloride in 20cc. water

= 0·4012g.

Gave α_D + 0·61°

Therefore $[\alpha]_D$ = + 15·26° (c. 2·0060, H_2O).

[C]. d-neo-Menthyl-trimethylammonium iodide and d-neomenthyl-trimethylammonium hydroxide.

(a) Preparation of d-neomenthyl-trimethylammonium iodide.

70g. of d-neomenthylamine, liberated from a specimen of the hydrochloride having $[\alpha]_D$ + 20·8° (c. 2·0, H_2O), was dissolved in 100cc. of methyl alcohol (magnesium dried) in a litre-round-bottom flask and 64·1g. (1 mol.) methyl iodide added. The mixture was boiled gently under reflux for one hour. 10·4g. (1 atom) of sodium in 120cc. of methyl alcohol were then added and the contents boiled for ten minutes. A further 64·1g. of methyl iodide were added and, after boiling for ten minutes, 10·4g. of sodium in 120cc. methyl alcohol and the contents boiled for a further ten minutes. At this point an oily basic layer separated out. Just sufficient methyl alcohol was added to make the mixture homogeneous, then another 64·1g. methyl iodide added and the mixture refluxed for one hour. 10·4g. of sodium in 120cc. methyl alcohol were added to the hot solution, the contents of the flask transferred to a 2-litre round-bottom flask and submitted to a vigorous steam-distillation to remove any unchanged or partially methylated base. On allowing to cool, the quaternary iodide came down from the

alkaline solution in beautiful plates. The iodide is stable in alkaline solution and is less soluble in alkaline solution than in water. After leaving overnight in the ice-chamber, the crystals were filtered off and dried on a porous plate. Yield: 122g. (83% theory). Recrystallisation from acetone was found to be more satisfactory than recrystallisation from water. The iodide came down from acetone on slow evaporation in large white prisms, m.p. 160·5° under decomposition and $[\alpha]_D$ -19·5° (c. 2·0, H_2O).

In alcoholic solution, d-neomenthyl-trimethylammonium iodide took up one molecular proportion of iodine, giving the triiodide. Recrystallisation from absolute alcohol gave dark violet plates, m.p. 107°. The triiodide was readily soluble in acetone, but less soluble in other organic solvents. It was unstable in alkali, decomposing to give back the stable monoiodide.

(b) Dry distillation of d-neomenthyl-trimethylammonium iodide.

20g. of pure d-neomenthyl-trimethylammonium iodide were placed in a small distilling flask and dry distilled under diminished pressure. The iodide decomposed at 155-160° (bath temperature) under 20mm. pressure. Menthene distilled over and was collected in a well-cooled receiver (8·4g.). The solid left in

the flask was shown to be trimethylamine hydriodide. The menthene was taken up in ether, the ether solution washed with dilute hydrochloric acid, then with water. After drying over anhydrous sodium sulphate, the ether was distilled off under diminished pressure and the menthene distilled. The menthene had b.p. 59°/10mm. α_D + 80·66° (1dm. homog.) and $n_D^{16°}$ 1·4532.

(c) Preparation and dry distillation of d-neomenthyl-trimethylammonium hydroxide.

Freshly prepared, well-washed silver oxide, made by treating 16g. of silver nitrate with barium hydroxide, was covered with water and a solution of 20g. d-neomenthyl-trimethylammonium iodide in water added. This was submitted to steam-distillation, but no decomposition occurred at this temperature. Accordingly the insoluble material was filtered off and the filtrate evaporated to dryness on the waterbath. The syrupy material so obtained was dried on a vacuum desiccator over phosphorous pentoxide and solidified to a colourless crystalline solid, which was extremely deliquescent. This was transferred to a distilling flask and distilled under diminished pressure. Under a pressure of 15mm. the hydroxide decomposed at 150-160°

(bath temperature) and menthene, water and trimethylamine distilled over, most of the trimethylamine escaping. The menthene was collected in a well-cooled receiver. The distillate was shaken with ether and the ether solution washed with dilute hydrochloric acid, followed by water. After drying over anhydrous sodium sulphate, the ether was evaporated off and the product distilled under diminished pressure. 8·1g. menthene (95% theory) were obtained. The menthene had the following physical constants:-

B.p.	57°/10mm.
$n_D^{20°}$	1·4520
$D_4^{20°}$	0·8122
$\alpha_D^{20°}$	+91·84° (1dm. homog.)
$[\alpha]_D^{20°}$	+112·9°
$[\alpha]_D$	+108·5° (c. 1·6365, abs. alcohol)
$[\alpha]_D$	+112·9° (c. 2·6915, ether)
$[R_L]_D$	Found:- 45·92
	Calculated:- 45·63

(d) Dry distillation of d-neomenthyl-trimethyl-ammonium hydroxide under ordinary atmospheric pressure.

20g. of d-neomenthyl-trimethylammonium iodide were converted into the quaternary hydroxide with moist silver oxide and distilled under ordinary pressure from an oil bath. At 150° (bath temperature) decomposition commenced and water and trimethylamine distilled over. When the bath temperature reached 175°, menthene began to come over rapidly. The bath temperature was allowed to rise to 180°. At this temperature all the menthene had distilled over and the distilling flask was completely empty. The menthene so obtained was purified as before and found to be identical with that obtained by distillation of the hydroxide under diminished pressure. The yield was quantitative.

2. Methylation of l-menthylamine.

[A]. N-Methyl-l-menthylamine.

(a) l-Menthone oxime.

(c.f. Galloway, Dissertation.
St. Andrews, 1935, p. 192).

100g. crystalline sodium acetate and 46g. hydroxylamine hydrochloride were dissolved in 170cc. of hot water, the solution filtered and allowed to cool down to 40°. A solution of 97cc. l-menthone (α_D -26·5) in 600cc. methyl alcohol was then added, with vigorous stirring, and the resulting clear solution allowed to stand. After a few hours, the first crop of crystals of l-menthone oxime was removed by filtration. A further crop of crystals was obtained from the mother-liquor on allowing it to evaporate slowly at room temperature. The total yield obtained was 65g. of long, slender needles having m.p. 58° and $[\alpha]_D$ -39·6° (c. 1·95, abs. alcohol).

(b) l-Menthylamine hydrochloride.

(c.f. Annalen. 276, 360, [1893] and
J.C.S. 1926, 2221).

50g. l-menthone oxime were dissolved in 750cc. dry absolute alcohol (dried over quicklime and freshly

distilled). The solution was heated to boiling and 75g. clean, dry sodium added gradually in small portions over a period of some two hours. When all the sodium had disappeared, water was added carefully to the hot liquid till the first vigorous reaction had ceased. The solution was then steam-distilled, the alcohol and aqueous fractions being collected separately. The aqueous portion was neutralised with dilute hydrochloric acid, the solution shaken once with ether to remove any unchanged oxime and then evaporated to dryness on the waterbath. The yield from this reaction averaged 45-50g. hydrochloride, having $[\alpha]_D$ -32·5° (c. 2·0, H_2O). One recrystallisation from water gave $[\alpha]_D$ -35·8°. This material was used for the next stage.

(c) l-Menthylglycine.

(i) Ethyl-l-menthylglycine.

To 120g. (2·5 mols.) of l-menthylamine hydrochloride dissolved in water was added sufficient 2N. sodium hydroxide solution to liberate the base, which was extracted with ether. The ether solution was washed twice with water, dried over anhydrous sodium sulphate and the ether distilled off under diminished pressure in a 1-litre round-bottom flask. To the pure l-menthylamine so obtained was added 30g. (1 mol.) of

ethyl chloroacetate and the solution was heated under a reflux condenser closed with a soda-lime tube on an oil bath at 130° for four hours.

(ii) Hydrolysis of ethyl-l-menthylglycine.

When reaction (i) was complete, 750cc. of 5% methyl alcoholic caustic potash were added, the contents transferred to a 2-litre flask and boiled gently on the waterbath for two hours.

(iii) Isolation of l-menthylglycine.

The alcohol and unreacted l-menthylamine were steam-distilled away from the product and the base recovered as hydrochloride (82g.). The aqueous solution was concentrated to about 250cc., cooled in ice and carbon dioxide passed in. The creamy-white solid which separated was filtered off, washed with a little ice-cold water, drained with suction at the pump and dried in the oven. The filtrate was further concentrated and carbon dioxide passed in again, giving a further yield of l-menthylglycine. The total yield of l-menthylglycine was 37·2g. (70% theory, calculated on weight of ethyl chloroacetate used). Recrystallisation from a little water gave small, white prisms, which had m.p. 191°, $[\alpha]_D$ -61·5° (c. 2·0, $CHCl_3$) and $[\alpha]_D$ -63·4° (c. 1·3970, H_2O).

N.B. From the above results, a comparison can be made between the reactivity of the amino-group of d-neomenthylamine and l-menthylamine, with $Cl\text{-}CH_2\text{-}COOEt$.

Found:- d-neo l.

(d) N-Methyl-l-menthylamine hydrochloride and 1,4-di-l-menthyl-2,5-dioxypiperazine.

(i) N-Methyl-l-menthylamine hydrochloride.

40g. of l-menthylglycine were heated in a round-bottom flask fitted with an air condenser on an oil-bath at 210° (bath temperature). The substance melted with effervescence, carbon dioxide and steam being evolved. When the reaction had ceased (1 hour) 20cc. of 2N. sodium hydroxide solution were added and the contents of the flask submitted to steam-distillation. A colourless refractive oil rapidly passed over with the steam. The base was isolated as hydrochloride (23·5g. - 60% theory). On recrystallisation from a little water it was obtained as colourless prisms, slightly hygroscopic, having m.p. 168° and $[\alpha]_D$ -52·75° (c. 2·0, H_2O).

Analysis:

Found:- Cl. 17·6%.

$C_{11}H_{24}NCl$ requires:- Cl. 17·8%.

(ii) 1,4-di-l-Menthyl-2,5-dioxypiperazine.

After steam-distilling away the N-methyl-l-menthylamine, a sticky mass remained in the flask. This was filtered off, pressed out under suction and dried on a porous plate. The material so obtained was taken up in hot methyl alcohol, from which it came down in white needles on cooling (10·9g.). Recrystallisation from methyl alcohol gave small, white needles, m.p. 201-2° under decomposition and $[\alpha]_D$ -106·25° (c. 2·0, $CHCl_3$). The substance was found to contain nitrogen by Lassaigne's Test. It gave no residue on ignition, was insoluble in water, dilute acids and alkali, only slightly soluble in ether, but very soluble in chloroform.

Analysis:

Found:- C. 73·9%, H. 10·6%, N. 7·2%.

$C_{24}H_{42}O_2N_2$ requires:- C. 73·8%, H. 10·8%, N. 7·2%.

(e) N-Methyl-l-menthylamine.

20g. of N-methyl-l-menthylamine hydrochloride were dissolved in water and the base liberated with dilute sodium hydroxide solution. The N-methyl-l-menthylamine was extracted with ether, the ether solution washed with water and dried over caustic potash.

After evaporating off the ether, the base was fractionated under diminished pressure. 15·6g. of pure N-methyl-l-menthylamine were obtained.

Physical Constants of N-methyl-l-menthylamine.

B.p.	87°/12mm.
$D_4^{17°}$	0·8531
$n_D^{17°}$	1·4587
$\alpha_D^{17°}$	-66·78° (1dm. homog.)
$[\alpha]_D^{17°}$	-78·28°
$[\alpha]_D^{17°}$	-69·17° (c. 2·0240, $CHCl_3$)
$[R_L]_D$	Found:- 54·12.
	Calculated:- 54·63.

Derivatives.

(i) Benzoyl-N-methyl-l-menthylamine.

To a solution of 2·0g. N-methyl-l-menthylamine in 5cc. of freshly distilled pyridine were added 2·0g. benzoyl chloride. The solution was left at room temperature for two days and was then poured into 50cc. 2N. hydrochloric acid. The red syrup which separated

was extracted with ether. The ether extract was washed once with dilute sulphuric acid and repeatedly with dilute sodium hydroxide solution until the red colour was removed from the solution. It was finally washed with water, dried and fractionated. A yellow syrup was obtained, which crystallised spontaneously after about a week at room temperature. Recrystallisation from a little methyl alcohol gave colourless needles, m.p. 65° and $[\alpha]_D$ -32·4° (c. 2·0, $CHCl_3$).

Analysis:

Found:-		C.	78·4%,	H.	9·9%.
$C_{18}H_{27}ON$	requires:-	C.	79·1%,	H.	9·9%.

(ii) p-Toluenesulphonyl-N-methyl-l-menthylamine.

This derivative was prepared in the same way as the above and was obtained in the form of colourless needles from methyl alcohol. It had m.p. 61° and $[\alpha]_D$ -37·5° (c. 2·0, $CHCl_3$).

Analysis:

Found:-		C.	65·8%,	H.	8·9%.
$C_{18}H_{29}O_2NS$	requires:-	C.	66·9%,	H.	9·0%.

(iii) N-methyl-l-menthylnitrosamine.

To a solution of 3·2g. N-methyl-l-menthylamine in 10cc. of dilute hydrochloric acid was added a solution of 2·5g. sodium nitrite in 10cc. of water. The product, a brown oil, was extracted with ether, the ether solution washed with water and dried over anhydrous sodium sulphate. On fractional distillation a pale yellow liquid was obtained (3g.) which crystallised on cooling in a freezing mixture. It was found to be very soluble in all organic solvents. Recrystallisation from a little methyl alcohol at 0° gave 2·2g. of pale yellow prisms, having m.p. 30·5°, $[\alpha]_D$ -39·5° (c. 2·0, $CHCl_3$) and $[\alpha]_D$ -54·0° (c. 2·3, benzene).

Analysis:

Found:-		C.	66·9%,	H.	11·3%.
$C_{11}H_{22}ON_2$	requires:-	C.	66·6%,	H.	11·1%.

[B]. N-di-Methyl-l-menthylamine.

(a) N-Methyl-l-menthylglycine.

(i) Ethyl-N-methyl-l-menthylglycine.

22g. (2·5 mols.) of pure N-methyl-l-menthylamine hydrochloride were dissolved in a minimum of water and the secondary base liberated with 2N. sodium hydroxide solution. The N-methyl-l-menthylamine was extracted with ether, the ether solution washed thoroughly with water and dried over anhydrous sodium sulphate. The ether was evaporated off under diminished pressure in a 500cc. round-bottom flask and 5g. (1 mol.) ethyl chloroacetate added. The mixture was refluxed gently at 140° on an oil bath for six hours.

(ii) Hydrolysis of ethyl-N-methyl-l-menthylglycine.

When reaction (i) was complete, 150cc. of 5% methyl alcoholic potassium hydroxide solution were added and the mixture boiled gently for two hours on the water-bath.

(iii) Isolation of N-methyl-l-menthylglycine.

The alcohol and excess base were removed by steam-distillation and the N-methyl-l-menthylamine recovered as hydrochloride (12·8g.). The aqueous solution was concentrated to small bulk, cooled in ice

and carbon dioxide passed through. No precipitate formed. Hence again N-methyl-l-menthylglycine is more soluble in water than the corresponding l-menthylglycine. The solution was accordingly acidified with dilute hydrochloric acid and evaporated to dryness. The inorganic part of the residue was removed by extracting the organic part with chloroform and filtering. The chloroform was evaporated off leaving a solid. This gave no residue on ignition but had a strong chlorine ion reaction. Lassaigne's test gave nitrogen and chlorine. The substance therefore appeared to be N-methyl-l-menthylamine hydrochloride. The free glycine compound was obtained as follows:-

The hydrochloride was dissolved in a minimum of water and the glycine precipitated as its insoluble calcium salt with calcium hydroxide solution. The calcium salt was filtered, washed thoroughly with water, then with a little alcohol and dried in a steam oven. It was a white, amorphous solid, weight 9·12g. The calcium salt was suspended in a little water and treated with the calculated quantity of sulphuric acid (37cc. N. H_2SO_4). The flask was stoppered and thoroughly shaken till the evolution of heat had ceased. An equal volume of absolute alcohol was then added and the insoluble calcium sulphate removed by filtration. The filtrate

was evaporated to dryness, when N-methyl-l-menthylglycine was obtained. Weight: 8·2g. (88% theory, calculated on weight of chloroacetate ester). Recrystallisation from toluene gave 7·1g. of small, colourless prisms, which were slightly hygroscopic. The dried material had m.p. 148° and $[\alpha]_D$ -51·5° (c. 2·0, H_2O).

Analysis:

4·537mg. dried at 100° in vacuo lost 0·294mg. H_2O 6.5%

$C_{10}H_{19}N(CH_3)CH_2\text{-}COOH.1H_2O$ has H_2O 7·4%

Dried material gave:- C. 68·8%, H. 10·8%.

$C_{13}H_{25}O_2N$ requires:- C. 68·7%, H. 11·0%.

N.B. Probably on standing longer in contact with the air N-methyl-l-menthylglycine would take up more water to form a stable dihydrate, c.f. analysis figures for N-methyl-d-neomenthylglycine. The first analysis gave low values for C and H, which led to the suspicion that the substance might be hygroscopic. These low values corresponded to a water content of between 1/2 H_2O - 1 H_2O. The second analysis gave value 2 H_2O. This suggests that these substances only take up water very slowly and have to stand quite a considerable time in contact with the air before reaching a stable state.

(b) Decomposition of N-methyl-l-menthylglycine. Formation of N-dimethyl-l-menthylamine.

5g. of N-methyl-l-menthylglycine were heated on an oil bath to 200° (bath temperature) in a small round-bottom flask fitted with an air condenser. The substance melted with effervescence, but no dimethylamine was detected. The temperature was maintained at 200° for one hour. The contents of the flask were then cooled and treated with 5cc. 2N. sodium hydroxide solution. The colourless refractive oil so obtained was extracted with ether, the ether solution washed twice with water and dried over anhydrous sodium sulphate. Fractionation gave an almost quantitative yield of N-dimethyl-l-menthylamine (3·9g. 97·5% theory). The base had b.p. 90·5°/10mm., $\alpha_D^{17°}$ -51·18° (1dm. homog.) and $n_D^{17°}$ 1·4584. It was identical with the base obtained from the dry distillation of l-menthyltrimethylammonium iodide and l-menthyl-trimethylammonium hydroxide, c.f. [C] below.

(c) Characterisation of N-methyl-l-menthylamine.

(1) Formation of chloroplatinate.

0·6cc. base was dissolved in a minimum of dilute hydrochloric acid and a solution of 0·5g.

platinic chloride in hydrochloric acid added. The yellow precipitate was filtered, washed thoroughly with water, then with a little absolute alcohol and dried in a desiccator. The substance melted at 205-206° under decomposition.

Ignition gave:- Pt. 25·04%.

$[C_{10}H_{19}N(CH_3)H]_2PtCl_6$ requires:- Pt. 25·14%.

(ii) Preparation of quaternary iodide.

To 2cc. base dissolved in 5cc. methyl alcohol were added 2cc. of methyl iodide and the mixture refluxed gently for one hour. The alcohol and excess methyl iodide were evaporated off under diminished pressure. The quaternary iodide solidified in the flask. Recrystallisation from a little acetone gave colourless prisms, m.p. 190° and $[\alpha]_D$ -39·25° (c. 2·0, H_2O).

(iii) Physical constants of N-di-methyl-l-menthyl-amine.

B.p.	90-90·5°/10mm.
$n_D^{17°}$	1·4584
$D_4^{17°}$	0·8462
$\alpha_D^{17°}$	-51·18° (1dm. homog).

$[\alpha]_D^{17°}$ $-60\cdot48°$ (homog.)

$[\alpha]_D^{17°}$ $-59\cdot67°$ (c. 2·0110, $CHCl_3$)

$[R_L]_D$ Found:- 59·05.

Calculated:- 59·34.

(iv) Rotatory power of N-dimethyl-l-menthylamine hydrochloride.

To a weighed amount of pure N-dimethyl-l-menthylamine in a 20cc. polarimeter flask were added a few cc. of distilled water and the calculated quantity of standard hydrochloric acid solution added from a micro-burette. The flask was warmed gently on the waterbath until the contents were homogeneous. The flask was then allowed to cool to room temperature, made up to the mark with distilled water and the rotatory power determined in a 2dm. tube.

Results:- Wt. of N-dimethyl-l-menthylamine = 0·3581g.

Amount of hydrochloric acid required = 1·96cc. N. HCl.

Wt. of hydrochloride in 20cc. water = 0·4294g.

Gave α_D $-2\cdot15°$

Therefore $[\alpha]_D$ = $-50\cdot06°$ (c. 2·1470, H_2O)

[c]. 1-Menthyl-trimethylammonium iodide and 1-menthyl-trimethylammonium hydroxide.

(a) Preparation of 1-menthyl-trimethylammonium iodide.

75g. l-menthylamine, prepared from a specimen of the hydrochloride having $[\alpha]_D$ -35·9° (c. 2·0, H_2O), were dissolved in 100cc. methyl alcohol (magnesium dried) and 68·7g. (1 mol.) of methyl iodide added. The mixture was boiled under reflux for one hour in a litre-round-bottom flask. The flask was then cooled and 11·2g. (1 atom) sodium in 120cc. methyl alcohol added. Refluxing was continued for ten minutes, the flask cooled, 68·7g. methyl iodide added and refluxed gently for ten minutes. A further 11·2g. sodium in 120cc. methyl alcohol was then added. At this stage some tertiary base came out as an oily layer. The solution was made homogeneous with methyl alcohol and refluxed for ten minutes. After cooling, 68·7g. methyl iodide were added and the mixture refluxed for one hour. The solution was then treated with 11·2g. sodium in 120cc. methyl alcohol, transferred to a 2-litre round-bottom flask and steam-distilled. The alcohol and a little incompletely methylated base were thus removed and the iodide came down from the remaining aqueous alskaline solution in glistening white plates, on allowing to cool. After

leaving overnight, the crystals were filtered, washed with a little cold water and dried on a porous plate. Yield: 135·5g. (85% theory). The l-menthyl-trimethyl-ammonium iodide was also recrystallised from acetone and was obtained as large, colourless prisms, having m.p. 190° under decomposition and $[\alpha]_D$ -39·25° (c. 2·0, H_2O).

In alcoholic solution, l-menthyl-trimethyl-ammonium iodide takes up one molecular proportion of iodine giving the tri-iodide, $C_{10}H_{19}N(CH_3)_3I_3$. Recrystallisation from alcohol gave long, violet needles, m.p. 117-118°. The tri-iodide is not so soluble in organic solvents as the mono-iodide, with the exception of acetone in which it is more soluble. It is unstable in alkali, giving back the stable mono-iodide.

(b) Dry distillation of l-menthyl-trimethylammonium iodide.

20g. l-Menthyl-trimethylammonium iodide were placed in a small distilling flask and dry distilled from an oil bath under ordinary atmospheric pressure. When the bath temperature reached 190° decomposition commenced. The product of decomposition, a non-homogeneous liquid, was collected in a well-cooled receiver. The liquid was transferred to a separating funnel and shaken with dilute hydrochloric acid. The

insoluble portion was extracted with ether, the ether solution washed with dilute hydrochloric acid, then with water and dried over anhydrous sodium sulphate. On evaporating off the ether under diminished pressure and fractionating the product, a menthene (2·5g. - 29·4% theory) was obtained having $\alpha_D^{20°}$ + 75·24° (1dm. homog.) and $n_D^{20°}$ 1·4522.

The acid solution from the above extraction was made alkaline with dilute caustic soda solution, when a colourless refractive oil came out. This was extracted with ether, the ether solution washed thoroughly with water to remove any trimethylamine and dried over caustic potash. The ether was then evaporated off under diminished pressure and on distilling the residue under diminished pressure, the base came over at 100°/18mm. (7·5g. - 66·4% theory). The base had α_D -51·16° (1dm. homog.) and $n_D^{18·5°}$ 1·4582. The base was shown to be N-dimethyl-l-menthylamine, c.f. [B] above, section (b).

(c) Preparation and dry distillation of l-menthyltrimethylammonium hydroxide.

Freshly prepared, well-washed silver oxide, made by treating 16g. silver nitrate with barium hydroxide, was covered with water and a solution of

20g. l-menthyl-trimethylammonium iodide in water added. After filtering off the precipitated silver iodide, the filtrate was evaporated to a syrupy liquid on the water-bath and dried in a vacuum desiccator over phosphorous pentoxide. The resulting deliquescent crystals of l-menthyl-trimethylammonium hydroxide were dry distilled under diminished pressure. Decomposition occurred at 165-170° (bath temperature) under 10mm. The distillate was collected in a well-cooled receiver and the menthene and basic portions separated as before. 2·6g. menthene (30% theory) and 7·7g. base (68·5% theory) were obtained.

Physical constants of menthene.

B.p.	56°/10mm.	
$n_D^{17°}$	1·4520.	
$D_4^{17°}$	0·8149.	
$\alpha_D^{17°}$	+107·34°	(1dm. homog.)
$[\alpha]_D^{17°}$	+131·7°	(homog.)
$[\alpha]_D$	+149·7°	(c. 1·6365, abs. alcohol)
$[\alpha]_D$	+149·2°	(c. 2·1585, ether)
$[R_L]_D$	Found:-	45·72
	Calculated:-	45·63

The base was again shown to be N-dimethyl-l-menthylamine. It had b.p. 90-90·5°/10mm., $n_D^{17°}$ 1·4584 and $\alpha_D^{17°}$ -51·18° (1dm. homog.).

(d) Dry distillation of l-menthyl-trimethylammonium hydroxide under ordinary atmospheric pressure.

20g. l-menthyl-trimethylammonium iodide were converted into the hydroxide with moist silver oxide and distilled under ordinary pressure from an oil bath. At 170° (bath temperature) decomposition began, water, trimethylamine and a little menthene distilling over. The bulk of the menthene came over between 175-185°. On allowing the temperature to rise slowly, no further liquid came over until the temperature of the bath reached 215°. The base came over between 215-235°. The menthene and base were separated as before and found to be identical with the specimens obtained from dry distillation of the quaternary hydroxide under reduced pressure. The relative proportions of menthene and base also remained unchanged at 30% menthene and 70% base.

3. Methylation of dl-piperitylamine.

[A]. N-Methyl-dl-piperitylamine.

(a) 'Hydrated Azine' of dl-piperitone.

To a solution of 100g. sodium hydroxide in 100cc. of water in a 2-litre round-bottom flask, ·162g. of powdered hydrazine sulphate were added in small amounts with constant shaking. The flask was kept well cooled under the water-tap to prevent any rise of temperature. At the end of the reaction no particles of hydrazine sulphate should be visible and the contents of the flask should have attained a creamy consistency. 400cc. methylated spirits were then added and the mixture boiled for ten minutes on the waterbath. 152g. dl-piperitone were then poured in and the whole refluxed for eight hours. The pale yellow solution was allowed to stand overnight and the sodium sulphate removed by filtration. The filtrate was steam-distilled to remove the alcohol and excess dl-piperitone and the residue extracted with ether. The ether-extract was washed once with water and dried by allowing to stand over anhydrous calcium chloride for at least two days. On removing the ether from a boiling waterbath in vacuo the product was obtained as a light-brown syrup containing

small globules of water. The yield averaged 140-145g.

(b) Reduction of the 'Hydrated Azine'. Preparation of dl-piperitylamine.

Reduction of the above syrup with pure zinc powder and glacial acetic acid yielded a mixture of dl-piperitylamine and neutral oil. The maximum yield of base was obtained by carrying out the reduction in the following manner:-

70g. freshly prepared hydrated azine were dissolved in 250cc. warm glacial acetic acid and transferred to a wide-mouthed 1-litre flask. A further 50cc. glacial acetic acid were used to wash in the solution. The flask was fitted with a three-holed bung carrying a stirrer with a mercury seal, an air condenser of about one foot in length and a smaller tube through which the zinc powder was added. The flask was immersed in a bath of water at 40° and stirring commenced. 80g. of pure zinc powder was then added in small portions over about half an hour, in such a manner that the bath temperature was maintained at between 40-50°. When all the zinc had been added the waterbath was raised to boiling point and maintained at that temperature for two hours. Vigorous stirring with a mechanical stirrer was maintained throughout. The mixture was then diluted with

500cc. hot water and the excess zinc (pyrophoric) removed by filtration. The filtrate was rendered just alkaline with concentrated sodium hydroxide solution and steam-distilled. The distillate was acidified with dilute hydrochloric acid and the neutral oil extracted with ether. The aqueous layer was then basified and the base extracted with ether. On drying and fractionating, crude dl-piperitylamine was obtained, b.p. 96-98°/15mm. The yield averaged 40g.

(c) dl-Piperitylglycine.

Attempted preparation by normal method.

(i) Ethyl-dl-piperitylglycine.

57·5g. (2·5 mols.) dl-piperitylamine, α_D - 0·35° (1dm. homog.), were condensed with 18·5g. (1 mol.) ethyl chloroacetate for two and a half hours on an oil bath at 165-170° in a flask carrying a reflux condenser fitted with a soda-lime tube.

(ii) Hydrolysis of ethyl-dl-piperitylglycine.

When reaction (i) was completed, 550cc. of 5% methyl alcoholic potassium hydroxide [i.e. sufficient to hydrolyse the ester and to neutralise the hydrochloric acid formed in reaction (i)] were added and the mixture refluxed on a waterbath for two hours.

(iii) Attempted isolation of dl-piperitylglycine.

The unreacted dl-piperitylamine was steam-distilled away from the product and recovered as the hydrochloride (35g.). The aqueous solution remaining was concentrated to about 200cc., cooled in ice and carbon dioxide passed in. No precipitate of dl-piperitylglycine formed. Evaporation of this solution to dryness yielded mainly the potassium salt, whereas neutralisation with hydrochloric acid and evaporation to dryness yielded the hydrochloride. It was not found possible to isolate the extremely soluble free glycine compound from either of these. Recourse was therefore had to a modified method of preparation.

Preparation by modified method.

(i) Ethyl-dl-piperitylglycine.

25·5g. dl-Piperitylamine (2 mols.) and 12·5g. ethyl chloroacetate (1 mol.) were heated together for eight hours in dry benzene. A white cake of dl-piperitylamine hydrochloride gradually formed. The benzene was distilled off under reduced pressure and the base hydrochloride removed by extraction with water. (Recovered - 13g.). The ester was taken up in ether, the ether extract washed with water, dried and fractionated.

The ester came over at 165°/20mm. Yield: 12·5g.

The ester was characterised as an acid oxalate. 2·4g. Ethyl-dl-piperitylglycine were dissolved in a minimum of hot alcohol and 0·9g. anhydrous oxalic acid in alcohol added. A white precipitate of the acid oxalate was immediately precipitated. On cooling, this was filtered, washed and dried. Yield: 3·1g., m.p. 184°. Two recrystallisations from alcohol gave beautiful needles, m.p. 189°.

Analysis:

Found:- C. 58·8%, H. 8·2%.

$C_{16}H_{27}NO_6$ requires:- C. 58·4%, H. 8·2%.

(ii) Hydrolysis of ethyl ester and isolation of dl-piperitylglycine.

7·4g. Ethyl-dl-piperitylglycine were hydrolysed with 50cc. (10% excess) 5% methyl alcoholic potassium hydroxide solution. After hydrolysis, the exact amount of 2N. hydrochloric acid (17·4cc.) required to neutralise the alkali used was added. The solution was then evaporated to dryness and the glycine extracted with chloroform. After removing the chloroform the dl-piperitylglycine was recrystallised from water, in which it is extremely soluble. Colourless prisms were

obtained, m.p. 180°.

Analysis:

Found:- C. 68·6%, H. 10·1%.

$C_{12}H_{21}NO_2$ requires:- C. 68·3%, H. 10·0%.

(d) Decomposition of dl-piperitylglycine. Formation of N-methyl-dl-piperitylamine.

2·6g. dl-Piperitylglycine were heated at 200° on an oil bath for one hour. Evolution of water and carbon dioxide occurred. The solution was rendered acid by addition of dilute hydrochloric acid and a small terpene fraction removed by steam-distillation. The residue was again basified and the N-methyl-dl-piperitylamine distilled over in steam. The base was extracted with ether, the ether extract dried over caustic potash and the ether evaporated off under diminished pressure. The yield of secondary base was extremely small.

(e) Characterisation of N-methyl-dl-piperitylamine. N-Methyl-dl-piperitylnitrosamine.

The small amount of N-methyl-dl-piperitylamine obtained above was dissolved in 5cc. 2N. hydrochloric acid and 0·6g. sodium nitrite in 5cc. water added. The resulting yellow oil was extracted with ether, the etherial solution washed with water and dried

over anhydrous sodium sulphate. On fractionation under diminished pressure, a pale yellow oil was obtained which crystallised after standing for some time in a freezing mixture. Recrystallisation from methyl alcohol at 0° gave light yellow prisms, m.p. 37°.

Analysis:

Found:- C. 67·37%, H. 10·24%.

$C_{11}H_{20}N_2O$ requires:- C. 67·35%, H. 10·20%.

[B]. N-diMethyl-dl-piperitylamine.

(a) Preparation of N-dimethyl-dl-piperitylamine.

25g. dl-Piperitylamine were dissolved in 40cc. methyl alcohol (magnesium dried) and 11·4cc. methyl iodide added. The mixture was refluxed for half an hour, 3·4g. sodium in 40cc. methyl alcohol added and refluxing continued for ten minutes. 11·4cc. Methyl iodide were then added, the mixture boiled for ten minutes and a further 3·4g. sodium in 40cc. methyl alcohol added. The whole was finally refluxed for one hour. After methylation, the excess methyl iodide and alcohol were removed by steam-distillation and the mixture of bases then distilled over in steam. To the distillate 170cc. (100%

excess) 2N. hydrochloric acid were added. The neutral oil which separated was removed by extraction with ether and the clear aqueous solution remaining concentrated down on the waterbath to about 250cc. This was then cooled in ice and a solution of 11·5g. sodium nitrite in 100cc. water allowed to drop in slowly. The solution was allowed to stand at room temperature for an hour, then heated gradually to 70° and maintained at that temperature for a further hour. The neutral oil was then steam-distilled off, the solution made alkaline and the tertiary base distilled over in steam. It was extracted with ether, the ether extract washed with water and dried over caustic potash. On evaporating off the ether under diminished pressure and fractionating the product, 10g. N-dimethyl-dl-piperitylamine were obtained. It had b.p. 88°/11mm., $n_D^{20°}$ 1·4705 and $\alpha_D^{20°}$ -1·62° (1dm. homog.).

(b) Characterisation of N-dimethyl-dl-piperitylamine.
Formation of chloroplatinate.

0·6cc. N-diMethyl-dl-piperitylamine was dissolved in a minimum of dilute hydrochloric acid and a solution of 0·5g. platinic chloride in dilute hydrochloric acid added. The yellow precipitate so obtained was filtered, washed with water and alcohol and dried in a

vacuum desiccator. The chloroplatinate had m.p. 175°

Ignition gave:-	Pt.	25·20%.
$[C_{10}H_{17}\text{-}N(CH_3)_2\text{-}H]_2PtCl_6$ requires:-	Pt.	25·27%.

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4. Methylation of d-piperitylamine.

[A]. N-Methyl-d-piperitylamine.

(a) Preparation of d-piperitylamine.

The d-piperitylamine used in this series of experiments was liberated from a specimen of d-piperitylamine-hydrogen-d-tartrate, having $[\alpha]_D$ + 50·0°, left by Walker and labelled 'Hanging solution II'. The base itself had α_D + 43·5° (1dm. homog.). The hydrochloride prepared from it had $[\alpha]_D$ + 67·25° (c. 2·0, H_2O) and recrystallisation of the hydrochloride from toluene raised this value to + 71·5°.

(b) d-Piperitylglycine.

(i) Ethyl-d-piperitylglycine.

76g. d-Piperitylamine were condensed with 34g. ethyl chloroacetate by refluxing in dry benzene for eight hours on the waterbath. The white cake of d-piperitylamine hydrochloride formed was washed out with water and recovered by evaporating the aqueous solution to dryness. 47g. were obtained, $[\alpha]_D$ + 67·25°. The benzene layer was washed thoroughly with water, dried over anhydrous sodium sulphate and fractionated. The yield of ester was 40·1g. It had b.p. 145-148°/12mm.,

α_D + 58·29° (1dm. homog.) and $n_D^{18°}$ 1·4755.

The ester was purified over the acid oxalate, prepared by adding an alcoholic solution of oxalic acid to a solution of the ester in alcohol. Recrystallisation from water gave fine needles, m.p. 195°.

Analysis:

Found:- C. 58·4%, H. 8·2%.

$C_{14}H_{25}NO_2$-$(COOH)_2$ requires:- C. 59·0%, H. 8·1%.

(ii) Hydrolysis of ethyl-d-piperitylglycine. Formation of d-piperitylglycine and l-α-phellandrene.

40g. Ethyl-d-piperitylglycine were hydrolysed with 270cc. 5% methyl alcoholic potassium hydroxide by refluxing for two hours on the waterbath. The solution was neutralised with the calculated quantity of standard hydrochloric acid. After neutralisation an oily layer separated on the solution. This was removed by steam-distillation, extracted with ether, the ether solution washed with water and dried over anhydrous sodium sulphate. On evporating off the ether, the residual liquid distilled over at 68°/22mm. It had a strong terpene smell and had α_D -43·24° (1dm. homog.) and $n_D^{14°}$ 1·4854. Qualitative experiments showed that a copious nitrosite could be obtained from as little as one drop of the

hydrocarbon, indicating that the product consisted essentially of l-α-phellandrene.

The aqueous layer, above, was evaporated to dryness and the free d-piperitylglycine separated from the inorganic residue by extraction with chloroform. On evaporating off the chloroform 29·2g. of glycine compound were obtained.

(c) Decomposition of d-piperitylglycine. Formation of N-methyl-d-piperitylamine and 1,4-di-d-piperityl-2,5-dioxypiperazine.

The d-piperitylglycine was decomposed by heating for two hours on an oil bath at 200-210°. The residue was acidified with dilute hydrochloric acid and the terpene fraction distilled over in steam. It was shown to consist essentially of α-terpinene. On basifying the solution and steam-distilling, a little N-methyl-d-piperitylamine passed over.

From the sticky residue left in the distilling flask after the base had been driven over a white solid was obtained after several recrystallisations from petroleum ether. It had m.p. 152° and $[\alpha]_D$ + 95·0° (c. 2·0, alcohol).

Analysis:

Found:-	C.	75·4%,	H.	9·9%.
$C_{24}H_{38}N_2O_2$ requires:-	C.	74·6%,	H.	9·9%.

(d) N-Methyl-d-piperitylamine hydrochloride.

The N-methyl-d-piperitylamine obtained from the decomposition of d-piperitylglycine was neutralised with dilute hydrochloric acid and isolated as the hydrochloride. The yield was 2·7g.. On recrystallisation from ethyl acetate, beautiful, fine, prismatic needles were obtained, having m.p. 180° and $[\alpha]_D$ +96·5° (c. 2·0, H_2O).

Analysis:

Found:-	C.	64·70%,	H.	10·60%.
$C_{11}H_{22}NCl$ requires:-	C.	64·86%,	H.	10·81%.

(e) N-Methyl-d-piperitylamine.

The base was liberated from the hydrochloride with dilute sodium hydroxide and extracted with ether. The ether solution was washed with water, dried over caustic potash and then fractionated. Pure N-methyl-d-piperitylamine was obtained. The following physical constants were observed for the base:-

B.p.	85·5°/10mm.
α_D	+79·2° (1dm. homog.)
$n_D^{14°}$	1·4770
$[\alpha]_D$	+119·9° (c. 2·435, $CHCl_3$)

[B]. N-diMethyl-d-piperitylamine.

(a) Preparation of N-dimethyl-d-piperitylamine.

40g. d-Piperitylamine were dissolved in 65cc. methyl alcohol (magnesium dried) and 16·5cc. (1 mol.) methyl iodide added. The mixture was refluxed for half an hour. 6·08g. (1 atom) sodium in 65cc. methyl alcohol were then added and refluxing continued for ten minutes. The mixture was then treated with a further 16·5cc. methyl iodide and refluxed for ten minutes before adding a final 6·08g. sodium in 65cc. methyl alcohol. The whole was then boiled for one hour. On completing the methylation, the alcohol and excess methyl iodide were removed by steam-distillation and the mixture of bases then distilled over in steam. This was acidified with 340cc. 2N. hydrochloric acid and the neutral oil which separated extracted twice with ether. The ether extract was dried and distilled under diminished pressure. Two main fractions were collected. The first fraction had b.p. 70-80°/16mm., α_D -32·10° (1dm. homog.) and $n_D^{15°}$ 1·4738. A copious nitrosite was obtained from a few drops of this fraction, which therefore appeared to consist essentially of l-α-phellandrene. The second fraction had b.p. 80-85°/16mm., α_D -18·94° (1dm. homog.) and $n_D^{15°}$ 1·4679. The nitrosite appeared only after a considerable time had elapsed. The

second fraction appeared to consist of l-α-phellandrene and α-terpinene. The acid solution was evaporated down to smaller bulk (about 300cc.) on the waterbath. This was then cooled in ice and a solution of 18·4g. sodium nitrite in 150cc. water added slowly with thorough shaking. The solution was allowed to warm slowly to room temperature and allowed to stand for one hour. The temperature was then raised to 70° and maintained there for a further hour. The small amount of neutral oil which formed was removed by steam-distillation. The residue was then basified and the liberated N-dimethyl-d-piperitylamine distilled over in steam. The base was purified as before, extracted with ether and dried over caustic potash. Fractionation gave 15g. N-dimethyl-d-piperitylamine, which had the following constants:-

B.p.	92°/12mm.
$n_D^{19°}$	1·4695
$\alpha_D^{20°}$	+110·12° (1dm. homog.)
$[\alpha]_D^{20°}$	+113·6° (c. 3·2040, $CHCl_3$)

(b) Characterisation of N-dimethyl-d-piperitylamine.

Formation of chloroplatinate.

0·6cc. N-diMethyl-d-piperitylamine was dissolved in a minimum of dilute hydrochloric acid and a solution of 0·5g. platinic chloride in dilute hydrochloric acid added. An orange-yellow precipitate of the chloroplatinate immediately formed. This was filtered, washed thoroughly with water, followed by absolute alcohol and dried in a vacuum desiccator. It had m.p. 171° under decomposition.

Ignition gave:- Pt. 25·18%.

$[C_{10}H_{17}\cdot N(CH_3)_2\cdot H]_2PtCl_6$ requires:- Pt. 25·27%.

5. Methylation of l-piperitylamine.

[A]. N-Methyl-l-piperitylamine.

(a) Preparation of l-piperitylamine.

75g. d-Tartaric acid were dissolved in 500cc. methylated spirits and 250cc. water by warming on the waterbath. To this warm solution was added a solution of 76·5g. freshly prepared dl-piperitylamine in 150cc. methylated spirits and the base washed in with a further 50cc. of warm methylated spirits. On allowing to cool, a crystalline separation occurred. This was filtered off, washed thoroughly with a mixture of water and methylated spirits of similar strength to the original liquor and dried on a porous plate. The l-piperitylamine hydrogen d-tartrate so obtained weighed 73g. and had $[\alpha]_D$ -40·0° (c. 1·4, H_2O). One recrystallisation from water gave $[\alpha]_D$ -47·14° (c. 1·4, H_2O) and a second recrystallisation raised this value to -47·8°.

The pure d-tartrate was suspended in water and the base liberated with excess sodium hydroxide. The base was extracted with ether, the ether solution dried over caustic potash and fractionated. Pure l-piperitylamine came over at 92°/15mm. It had α_D -81·38° (1dm. homog.). [Walker gives $\alpha_D^{18·5°}$ -75·94 and Read and Storey, J.C.S. 1930, 2777 give $\alpha_D^{15°}$ -71·31°.]

(b) l-Piperitylglycine.

(i) Ethyl-l-piperitylglycine.

24·2g. l-Piperitylamine [α_D -61·5° (1dm. homog.), liberated from a specimen of the d-tartrate having $[\alpha]_D$ -37·5° (hanging resolution)] were condensed with 10·7g. ethyl chloroacetate for eight hours in dry benzene. The hydrochloride was recovered as before by washing out with water (weight 13g.). The benzene solution was dried and fractionated, yielding 14·5g. of the ester, which had b.p. 163-165°/25mm., α_D -51·14° (1dm. homog.) and $n_D^{20°}$ 1·4733.

The ester was purified over the acid oxalate. Two recrystallisations from water gave white, prismatic needles, m.p. 196°.

Analysis:

Found:- C. 58·92%, H. 8·30%.

$C_{14}H_{25}NO_2(COOH)_2$ requires:- C. 58·36%, H. 8·21%.

Pure ethyl-l-piperitylglycine, liberated from the oxalate, had $\alpha_D^{17°}$ -83·14° (1dm. homog.) and $n_D^{17°}$ 1·4748.

(ii) Hydrolysis of ethyl-l-piperitylglycine.

Formation of l-piperitylglycine.

11·4g. of Ethyl-l-piperitylglycine were hydrolysed for two hours on the waterbath with 80cc. 5% methyl

alcoholic potassium hydroxide. The resulting alkaline solution was neutralised with the calculated amount of standard hydrochloric acid. The neutral solution was then evaporated to dryness and the free glycine extracted with chloroform. On evaporating off the chloroform, the glycine solidified to a sticky solid, which was extremely soluble in water.

(c) Decomposition of l-piperitylglycine. Formation of N-methyl-l-piperitylamine, 1,4-di-l-piperityl-2,5-dioxypiperazine and α-terpinene.

The l-piperitylglycine obtained above was heated at 190° for one hour on an oil bath. Decomposition occurred with formation of a neutral terpene fraction, a small amount of base and a solid residue of piperazine derivative. The neutral fraction was removed by steam-distillation from acid solution (5g.). It was practically optically inactive and gave no nitrosite. On basifying the residue and steam-distilling a small amount of N-methyl-l-piperitylamine was obtained. The residue after the steam-distillation contained an oily surface layer which solidified to a sticky solid. This was filtered off, washed as well as possible with water and recrystallised from aqueous alcohol. Sticky crystals were obtained, but after a further two recrystallisations from petroleum

ether the substance was sufficiently pure to be identified as 1,4-di-l-piperityl-2,5-dioxypiperazine. It recrystallised from this solvent in the form of small, white needles, m.p. 152° and $[\alpha]_D$ -113·3° (c. 1·783, alcohol).

Analysis:

Found:-		C.	75·6%,	H.	9·9%.
$C_{24}H_{38}N_2O_2$	requires:-	C.	74·6%,	H.	10·0%.

(d) N-Methyl-l-piperitylamine hydrochloride.

The base obtained from the steam-distillation above was neutralised with dilute hydrochloric acid and evaporated to dryness, yielding 0·7g. of the hydrochloride. Two recrystallisations from toluene gave beautiful, white needles, m.p. 180°, having $[\alpha]_D$ -96·7° (c. 1·982, H_2O).

Analysis:

Found:-		C.	64·80%,	H.	10·63%.
$C_{11}H_{22}NCl$	requires:-	C.	64·86%,	H.	10·81%.

Since recrystallisation of the N-methyl-l-piperitylamine hydrochloride above had reduced the already small yield to such proportions as to render liberation of the free base for the purpose of measuring its rotatory

power impracticable, an attempt was made to prepare this secondary base by methylation of pure l-piperitylamine using one molecular proportion of methyl iodide and one atom of sodium. The secondary base was liberated as the nitroso-compound, which was extracted with ether, the ether extract dried over anhydrous sodium sulphate and the ether then distilled off under diminished pressure. Hydrolysis of the nitrosamine by the method of Ladenburg (Ber. 12. 949, [1879]) with concentrated hydrochloric acid and gaseous hydrogen chloride resulted however in the production of a tarry oil by decomposition and no secondary base was obtained.

[B]. N-diMethyl-l-piperitylamine.

(a) Preparation of N-dimethyl-l-piperitylamine.

38g. l-Piperitylamine, having α_D -81·38° (1dm. homog.), were dissolved in 60cc. methyl alcohol (magnesium dried) and 15·7cc. methyl iodide added. The mixture was refluxed for half an hour, then 5·8g. sodium in 60cc. methyl alcohol added and refluxing continued for ten minutes. After similar treatment with a further 15·7cc. methyl iodide, a final 5·8g. of sodium in 60cc. methyl alcohol were added and the whole refluxed for an hour. The alcohol and excess methyl iodide were then removed

by steam-distillation, followed by the mixture of bases. These were acidified with 320cc. 2N. hydrochloric acid and the neutral oil which separated extracted with ether. After drying and evaporating off the ether, the residual liquid (13·5g.) was distilled under diminished pressure, two fractions being collected. The first had b.p. 70-80°/11mm., α_D +21·68° (1dm. homog.) and $n_D^{16°}$ 1·4716. It gave a copious nitrosite and consisted essentially of d-α-phellandrene. The higher boiling fraction, b.p. 80-85°/11mm. had α_D +20·84° (1dm. homog.) and $n_D^{16°}$ 1·4670. It gave no nitrosite.

The acid solution was evaporated to smaller bulk, cooled in ice and treated with a solution of 17·5g. sodium nitrite in 150cc. water, with constant shaking. After reaching room temperature the solution was allowed to stand for one hour, then heated to 70° and maintained at that temperature for a further hour. The small amount of neutral oil which had separated was removed by steam-distillation, and the N-dimethyl-l-piperitylamine liberated with alkali and driven over in steam. The base was extracted with ether, the ether extract being dried over caustic potash. Fractionation gave 14·5g. N-dimethyl-l-piperitylamine. The tertiary base had the following physical constants:-

B.p.	100°/17mm.
$a_D^{17°}$	-174·7° (1dm. homog.)

$n_D^{17°}$ 1·4715

$[\alpha]_D^{17°}$ -178·4° (c. 3·105, $CHCl_3$)

(b) Characterisation of N-dimethyl-l-piperitylamine.

0·6cc. N-diMethyl-l-piperitylamine was dissolved in a minimum of dilute hydrochloric acid and a solution of 0·5g. platinic chloride in hydrochloric acid added. The orange-yellow precipitate of the chloroplatinate was filtered off, washed with water and alcohol and dried in a vacuum desiccator. It had m.p. 165° under decomposition.

Ignition gave:- Pt. 25·32%.

$[C_{10}H_{17}\cdot N(CH_3)_2\cdot H]_2PtCl_6$ requires:- Pt. 25·27%.

(c) Rotatory power of N-dimethyl-l-piperitylamine hydrochloride.

The rotatory power of the hydrochloride was measured by weighing out a known amount of N-dimethyl-l-piperitylamine and acidifying with the required amount of standard hydrochloric acid, the solution being then made up to the mark with distilled water. The flask was heated gently on the waterbath till the solution was clear. The value obtained was $[\alpha]_D$ -83·2° (c. 1·983, H_2O).

6. Additional experiments.

Application of the method to the N-alkylation of aniline.

[A]. N-methylaniline.

(a) N-Phenylglycine.

c.f. Vanino. 1923, 2. 606. Also Meyer, Ber. 8. 1156 and Bischoff and Hausdörfer. Ber. 25, 2270.

(i) Ethyl-N-phenylglycine

To 46·5g. (2·5 mols.) aniline in a two-litre round-bottom flask were added 24·5g. (1 mol.) ethyl chloroacetate and the solution heated under a reflux condenser on an oil bath at 120-130° for four hours.

(ii) Hydrolysis of ethyl-N-phenylglycine.

When reaction (i) was complete, 700cc. of 5% methyl alcoholic potassium hydroxide (i.e. sufficient to hydrolyse the ester and neutralise the hydrochloric acid formed) were added and the mixture was boiled on a waterbath for two hours.

(iii) Isolation of N-phenylglycine.

The alcohol and unreacted aniline were steam-distilled away from the product. The aqueous solution (about 500cc. in volume) in the flask was evaporated

down on the waterbath to 250cc., cooled in ice-water and carbon dioxide passed in until the solution reacted distinctly acid to litmus. No separation of phenylglycine was observed. Hence phenylglycine is a stronger acid than carbonic acid and the P_H value of the solution is still too high, i.e. still alkaline to phenylglycine. On reducing the P_H value still further with dilute hydrochloric acid (2N), a creamy, whitish-brown solid came down. The phenylglycine was filtered off, washed with a little ice-cold water and dried in the oven. The mother-liquors were concentrated down a little further, when a little more phenylglycine was obtained. Yield: 20g. (66% theory). m.p. 126-127° (recrystallised from water).

(b) Decomposition of N-phenylglycine. Formation of monomethylaniline and 1,4-diphenyl-2,5-dioxypiperazine.

10g. of phenylglycine were heated in a small round-bottom flask in an oil bath. At bath temperature 130° the crystals melted without effervescence. The temperature was allowed to rise slwoly when slight effervescence appeared to take place and water-vapour was evolved which condensed on the sides of the flask. When the bath temperature reached 200°, the flask was removed,

allowed to cool and 5cc. 2N. sodium hydroxide added, followed by steam-distillation. A few drops of oil passed over with the steam and were collected in the receiver. This oil was shown to be monomethylaniline.

The main product of the reaction was however contained in the residue as a white solid. It was filtered off, washed with water, dried and recrystallised from absolute alcohol, in which it was not very soluble. It had m.p. 263° and was insoluble in water, acids and alkali. The substance was 1,4-diphenyl-2,5-dioxy-piperazine (Beilstein. Syst. 3587) formed by two glycine molecules condensing with elimination of two molecules of water. The yield was 6·3g. (71% theory).

[B]. N-diMethylaniline.

(a) N-methyl-phenylglycine.

c.f. Silberstein. Ber. 17, 2661; also Hinsberg Ber. 27, 3258.

(i) Ethyl-N-methyl-phenylglycine.

To 53·5g. (2·5 mols.) monomethylaniline in a two-litre round-bottom flask were added 24·5g. (1 mol.) ethyl chloroacetate and the solution was heated under a reflux condenser on an oil bath at 130° for three hours.

(ii) Hydrolysis of ethyl-N-methyl-phenylglycine.

When reaction (i) was completed, 700cc. of 5% methyl alcoholic caustic potash were added and the mixture boiled in a waterbath for two hours.

(iii) Isolation of N-methyl-phenylglycine.

The unreacted monomethylaniline and the alcohol were removed by steam-distillation. The aqueous solution was evaporated down to about 250cc. on the waterbath, cooled in ice and carbon dioxide passed in till the solution was acid to litmus. No precipitate formed. On acidification with dilute hydrochloric acid, N-methyl-phenylglycine came out as a thick liquid, heavier than water. This was extracted with chloroform, the chloroform solution washed thoroughly with water and dried over anhydrous sodium sulphate. On evaporating off the chloroform under reduced pressure, 24·5g. (73% theory) N-methyl-phenylglycine were obtained.

(b) Decomposition of N-methyl-phenylglycine.
Formation of dimethylaniline.

(i) It was shown that N-methyl-phenylglycine decomposes on distillation under ordinary pressure giving dimethylaniline.

(ii) Some of the liquid was digested with a little cold, concentrated hydrochloric acid. A crystalline hydrochloride was obtained. Recrystallisation from concentrated hydrochloric acid gave colourless prisms, very soluble in water, having m.p. 194-5°. When an aqueous solution of the hydrochloride was evaporated down slowly to dryness on the waterbath, a thick viscous liquid was obtained, which was very hygroscopic. This appeared to be dimethylaniline hydrochloride.

Attempts made to modify original condensation process.

An exhaustive series of experiments was carried out in an attempt to modify the condensation process. The method described is completely satisfactory, except in one respect, namely, that an excess of base has to be used to fix the hydrochloric acid formed. No loss of material is involved, but the preparation of large quantities of valuable bases is a disadvantage. Briefly, the idea was to find some inorganic base or basic salt, or, alternatively, some tertiary organic base, which would fix the hydrochloric acid liberated in the condensation process, without itself combining with the ethyl chloroacetate or otherwise influencing the reaction.

For this series of experiments aniline was used.

Molecular proportions of aniline and chloroacetic ester were condensed in the presence of various inorganic and organic bases. It will suffice to indicate the substances used and the results obtained.

(a) Anhydrous sodium carbonate. (solid).

The reaction proceeds normally, but the sodium chloride formed causes the reaction mixture to become solid and prevents the reaction from going to completion.

(b) Hydrated sodium acetate. i.e. in aqueous suspension. (c. 1908, I, 1006).

The reference merely states that the phenylglycine ester was obtained in good yield and excellent purity. The yield was found to be only of the order of 50%. This reaction was also carried out with d-neomenthylamine, but, from 50g. d-neomenthylamine hydrochloride and 32g. of ethyl chloroacetate, only 17g. of d-neomenthylglycine were obtained.

(c) Pyridine.

Tried alone and also in dry benzene. In both cases an addition compound was formed with the ethyl chloroacetate and this addition compound did not break up again at the temperature of the reaction.

(d) Quinoline.

Addition compound formed.

(e) Dimethylaniline.

Gave yields of less than 50%, probably due to an addition compound being formed. Hence no improvement on original method.

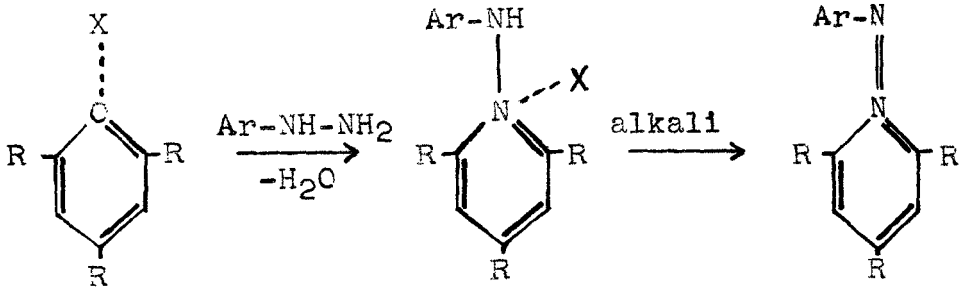
Attempts were also made to condense aniline directly with chloroacetic acid. The phenylglycine was precipitated immediately on formation in the form of an insoluble salt of a heavy metal. That is, molecular proportions of aniline and chloroacetic acid were condensed in saturated salt solution in the presence of oxides or carbonates of the heavy metals, such as hydrated ferrous oxide or ferrous carbonate. c.f. C. 1906. II. 1746. The phenylglycine salt, being insoluble in saturated salt solution, was precipitated, filtered off and decomposed with alkali. The yields were again unsatisfactory.

Part II.

A POSSIBLE METHOD OF DETERMINING THE EFFECTS OF SUBSTITUTION BY MEANS OF THE VELOCITY OF DECOLORISATION OF SUBSTITUTED PYRIDINE-ARYLIMINES.

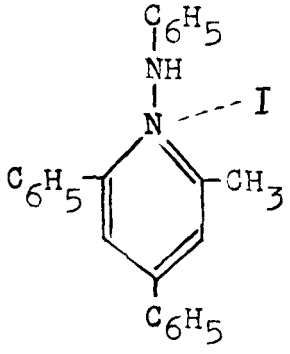
A. THEORETICAL

Pyridine-aryl-imines, discovered by W. Schneider, represent a novel type of intensely coloured bases, which are to be regarded as anhydrides of N-aryl-amino-pyridinium hydroxides. They can be obtained by condensation of pyrylium compounds with aryl-hydrazines and decomposition with alkali of the resulting pyridinium salts. By the use of substituted pyrylium salts on the one hand and substituted aryl-hydrazines on the other, a whole series of such anhydrobases has been prepared. c.f. W. Schneider. Über Pyridin-arylimine, I. Ann. 438, 115. (1924). Subsequent evidence suggests the following representation for the reaction:-

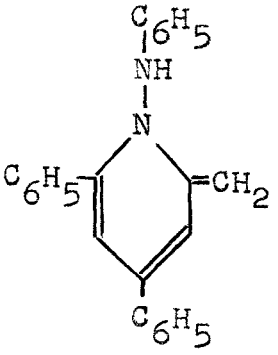


The pyridine-aryl-imines were discovered during investigations into the properties of 2-methyl-4,6-diphenyl-pyrylium iodide (V). Condensation of this compound with phenyl-hydrazine gave N-phenylamino-2-methyl-4,6-diphenyl-pyridinium iodide (I), which in turn

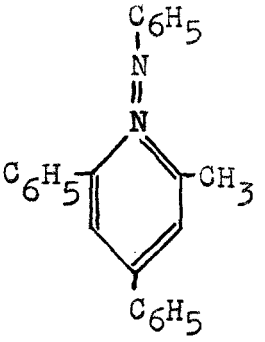
was found to give a deep violet anhydro-base on treatment with alkali. Two formulae (II and III) came into consideration for this anhydro-base.



I



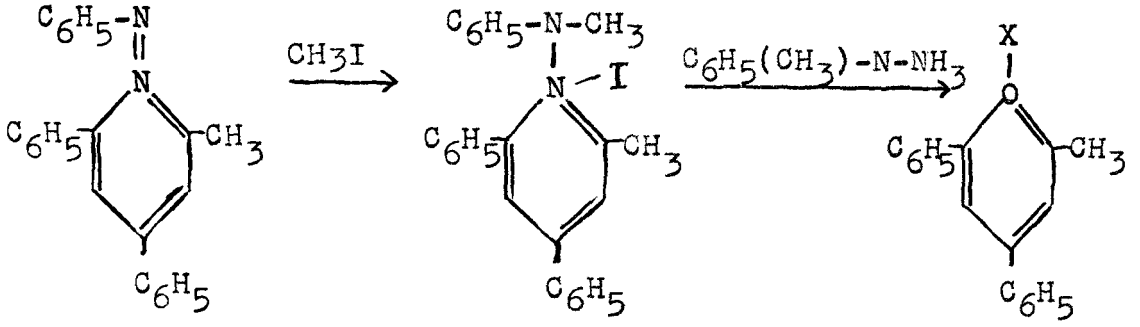
II



III

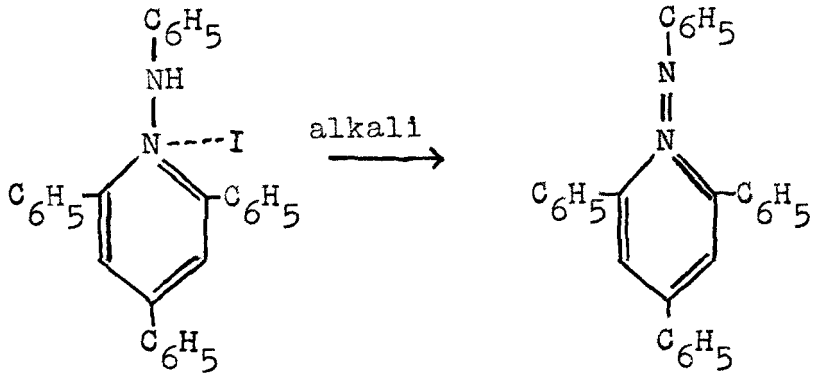
The chemical properties of the compound were in agreement with both formulae. Schneider was able to show, however, that the intense colour of the anhydro-base could not be explained from the methylene dihydro-pyridine form (II). c.f. Ann. 438, 115. (1924). The methylene dihydro-cyclamines are all amorphous, unstable substances, usually yellow in colour and not capable of being recrystallised . The anhydro-base in question was crystalline in form, relatively stable and of a much more intense colour. It could, moreover, be recrystallised. The behaviour of the substance on treatment with methyl iodide provided further strong evidence against formula II. An addition compound was isolated which was shown to be identical with N-(methyl-phenyl-amino)-2-methyl-4,6-diphenyl-pyridinium

iodide (IV) obtained by the action of methyl-phenyl-hydrazine on 2-methyl-4,6-diphenyl-pyrylium iodide (V). This reaction can however easily be explained from formula III.



III IV V

It would therefore appear that formula III should be ascribed to the anhydro-base. This conclusion received strong support when Leutheusser (Dissertation, Jena, 1924) succeeded in isolating an analogous deep-blue base (VI) from N-phenylamino-2,4,6-triphenyl-pyridinium iodide (VII).

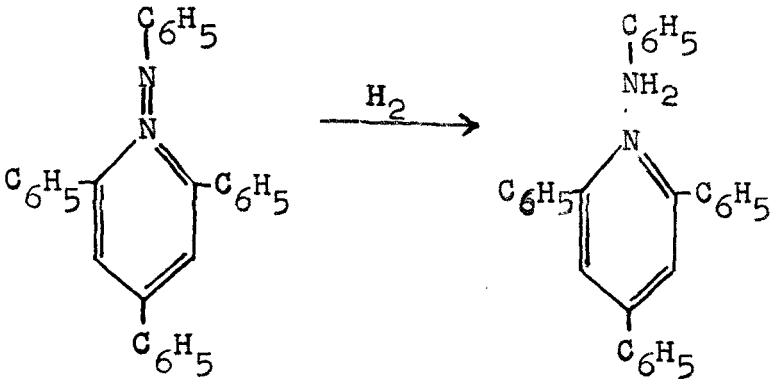


VII VI

As in this case no methylene dihydro-pyridine form is possible, the colour of the anhydro-base can only be explained by formula III, in which it may, at this stage, be said that the grouping -N =N ≡N is strongly chromophoric (see later).

From experiments involving treatment of the blue triphenyl-base (VI) with carbon disulphide and phenyl mustard oil, Schneider succeeded in demonstrating the presence of small amounts of 2,4,6-triphenyl-pyridine in the decolourised solutions. The formation of this compound is easily explained from the pyridine-imine structure, being caused simply by the splitting off of the $C_6H_5N=$ group. In one instance, using phenyl mustard oil, an indication as to what might happen to this group was obtained. Schneider isolated a red crystalline compound, of formula $C_{12}H_{10}NS$, and assumed that he had obtained a sulphur analogue of Wieland's diphenyl amino-oxide $(C_6H_5)_2NO$. This observation led him to investigate the effect of catalytic hydrogenation on these anhydro-bases. The blue solution of the base (VI) in methyl alcohol was decolourised by hydrogen, using platinum black as catalyst, within a few seconds. On breaking off the hydrolysis at the moment of complete decolourisation, a quantitative yield of triphenyl-pyridine was obtained, along with aniline from the

remaining $C_6H_5N=$ radical. This smooth decomposition of the pyridine-imine by catalytic hydrogenation is amply illustrated by the scheme:-



and provides further strong evidence for the constitution assigned to the base by Schneider. Since methyl-diphenyl-pyridine-imine behaves analogously on catalytic hydrogenation - yielding 2-methyl-4,6-diphenyl-pyridine and aniline - the pyridine-imine structure must also hold for this base and for all the other analogues.

From the reactions so far mentioned, it is evident that the pyridine-imine structure holds for these anhydro-bases, and that the intense colour of these substances in particular is due to such a structure. Nevertheless, these bases can also react in the tautomeric methylene dihydro-pyridine form, as is clearly indicated by the following considerations.

The two compounds, the methyl-diphenyl-base

(III) and the triphenyl base (VI), exhibit notable differences in their chemical and optical properties. The behaviour of the former towards carbon disulphide, phenyl mustard oil and phenyl isocyanate is totally different compared with the latter (c.f. Ann. 438, 115. 1924) and must be based on the tautomeric methylene dihydro-pyridine formula. The triphenyl base, moreover, is completely stable in all solvents and such solutions always show the same deep blue colour, whereas solutions of the methyl-diphenyl-base differ quite appreciably in colour according to the nature of the solvent and exhibit a more or less definite instability. This difference in optical properties is illustrated by the following table, compiled by Schneider and Trebitz.

Solvent	Methyl-diphenyl-base (III)		Triphenyl-base (VI)	
	a.	b.	a.	b.
Toluene	blue	blue	blue	blue
Chloroform	violet	red-lilac	blue	blue
Alcohol	red-lilac	fuchsine-red	blue	blue

a. Temperature of ether-carbon dioxide mixture.

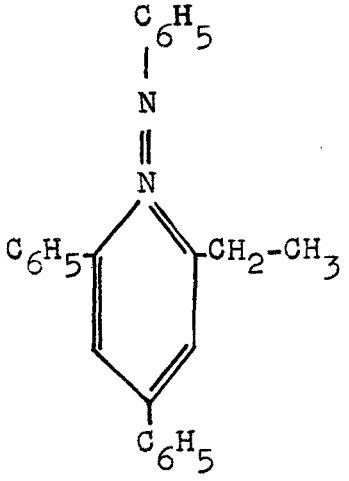
b. Temperature of liquid air.

These results can doubtless be explained by the fact that the base (III) can form solvates with certain solvents and that the changes in colour are due to "Solvatochromie". The solvate formation depends on increased addition of solvent molecules with increasing di-pole nature of the solvent and also on the temperature. The unchanged colour of the triphenyl base in all solvents indicates, however, that the constitution of the base itself plays a decisive part in the phenomenon. One is, therefore, forced to conclude that the capacity of the methyl-diphenyl-base for solvate formation is accounted for by the possibility of its desmotropic conversion into the methylene dihydro-pyridine form, which perhaps forms the desired structural state in the solvates. The triphenyl base, however, must react solely in the pyridine-imine form and therefore exhibits no "Solvatochromie".

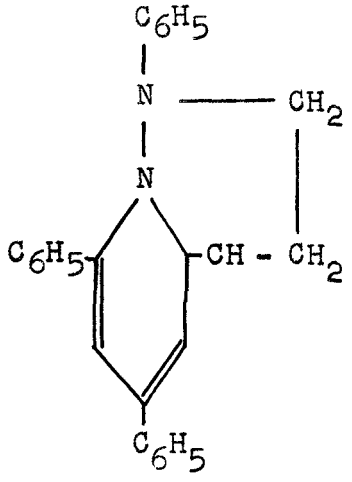
Intramolecular change undergone by the pyridine-aryl-imines.

It has already been mentioned that 2-methyl-4,6-diphenyl-pyridine N-phenylimine is unstable in solution. The characteristic colour fades after a relatively short time and reddish-brown solutions are

obtained, from which, until recently, no definite product had been isolated. On the other hand, in the case of two homologues of this pyridine-imine, it had already been found that these compounds undergo a conversion into colourless isomers. The first such case is described by G. Trebitz (Dissertation. Jena, 1922) who synthesised 2-ethyl-4,6-diphenyl-pyridine phenylimine (VIII). He thought the isomeric conversion of the blue ethyl base could be explained by reaction of the base in its ethylene dihydro-pyridine form, ring closure taking place between the nitrogen of the imino-group and one of the ethylene carbon atoms, yielding a pyrazolidine derivative (IX).

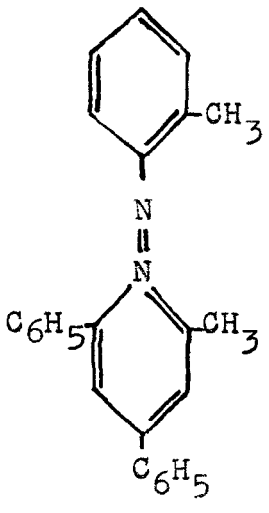


VIII

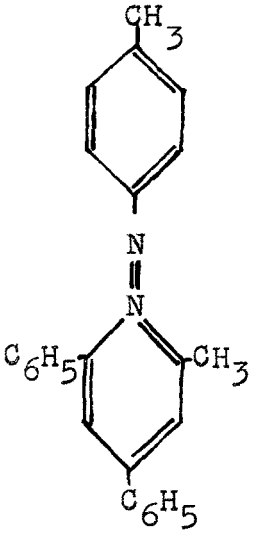


IX

It was later found by Görner (Dissertation. Jena, 1924) that 2-methyl-diphenyl-pyridine-N-O-and N-p-tolylimines (X and XI) undergo a conversion into colourless, isomeric substances.



X

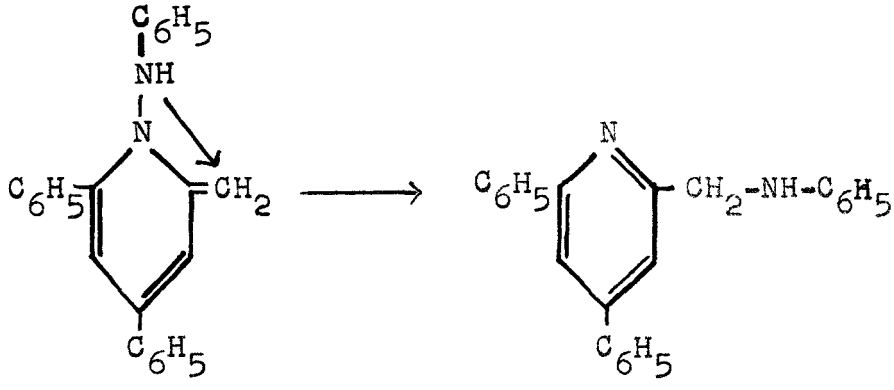


XI

This phenomenon was again irreversible. An analogous representation of the products was not so feasible in this case.

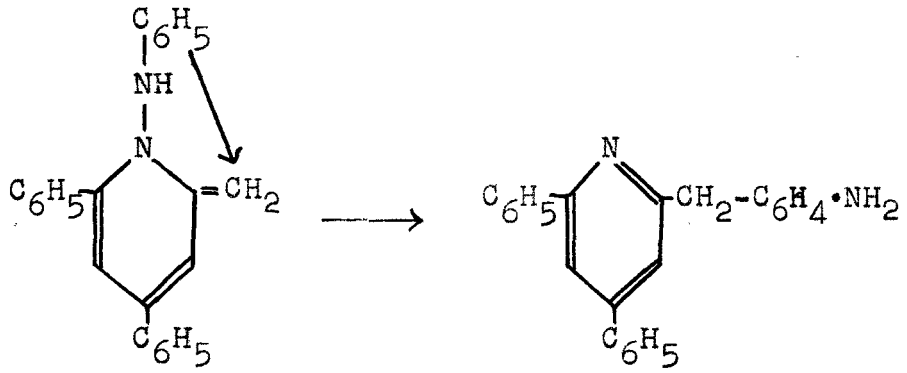
The fact that certain pyridine-imines give rise to substituted pyridines under certain conditions - c.f. action of carbon disulphide or catalytic hydrogenation on the 2,4,6-triphenyl compound (VI) above - led to the suspicion that the decolourisation of solutions of the methyl base (III) might be based on a similar decomposition with formation of methyl-diphenyl-pyridine. Schneider and Weiss (Ber. 61. II, 2445, [1928]) showed however that this was not the case,

but rather that alcoholic solutions of the blue base underwent intramolecular rearrangement with the formation of a colourless, isomeric, weakly basic substance. The formation of a ring compound as postulated by Trebitz was again improbable here, for such a ring would consist of only four members, two of which would be nitrogen and two carbon atoms, i.e. an exceedingly unstable system. After it was known, however, that the -N=N≡ grouping could be relatively easily broken, the consideration arose that the C_6H_5N= group might separate off and wander to the methyl carbon atom. This could be more easily explained if one were to suppose that the reaction occurred from the desmotropic methylene dihydropyridine formula (II), according to the following scheme:-



The product should therefore be a secondary base, possessing properties similar to, say, benzyl-aniline. This can be converted into a Schiff's base, benzylidene aniline, by careful oxidation and this in turn can be

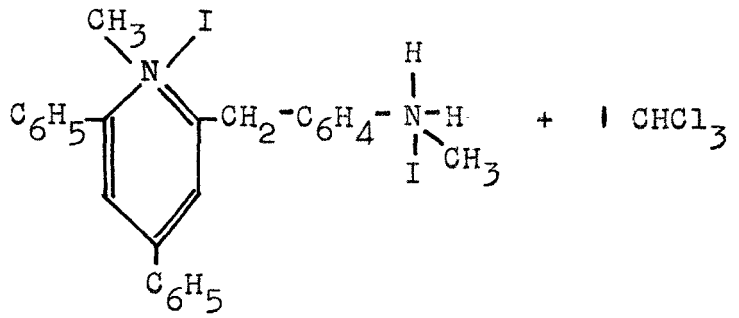
hydrolysed to benzaldehyde and aniline. Experiments to prepare a Schiff's base from the isomerisation product were entirely negative. Further, the behaviour of the substance towards nitrous acid showed that it was not a secondary base, as no nitrosamine was obtained. On the contrary, the resulting acid solution showed the properties of a diazonium solution and could be coupled with phenols. Although the resulting dyes could not be isolated in a pure state, suitable for analysis, no doubt was entertained as to their nature. Hence the product of the intramolecular change was to be regarded as a primary base and the intramolecular rearrangement itself as a conversion on the lines of the benzidine change, as indicated below.



Schneider and Weiss endeavoured to confirm this by removal of the amino-group by heating the diazotised solution with alcohol. They obtained a crystalline compound, the composition of which was not,

however, in agreement with the expected 2-benzyl-4,6-diphenyl-pyridine. They were unable to identify this compound. The author has since isolated this product in the pure state (see later) and shown it to be an indazole derivative of the isomerisation product.

Schneider and Weiss were therefore compelled to confirm their projected formula in other ways. Treatment with excess methyl iodide and evaporation to dryness yielded a resinous product. Further treatment with chloroform gave a crystalline compound, which on analysis appeared to have the formula XII,



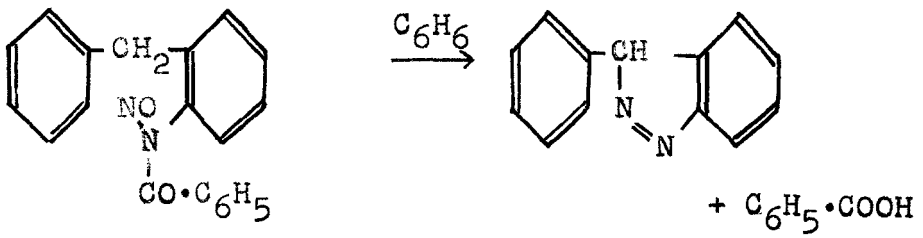
XII.

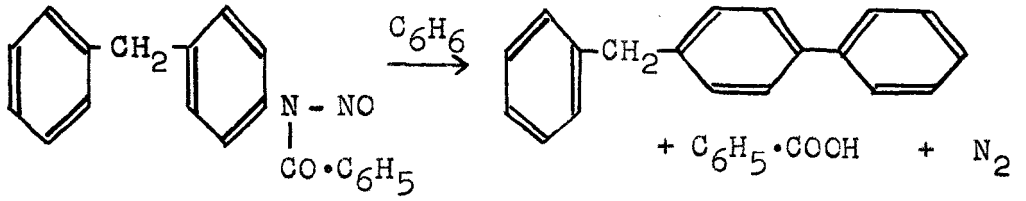
namely, a hydriodide of 2-methyl-amino-benzyl-4,6-diphenyl-pyridine methiodide, i.e. the hydriodide of a secondary base. Treatment of this salt with nitrous acid in glacial acetic acid gave an amorphous product, which gave a positive Liebermann's reaction and was therefore to be regarded as a nitrosamine.

These results, although not completely

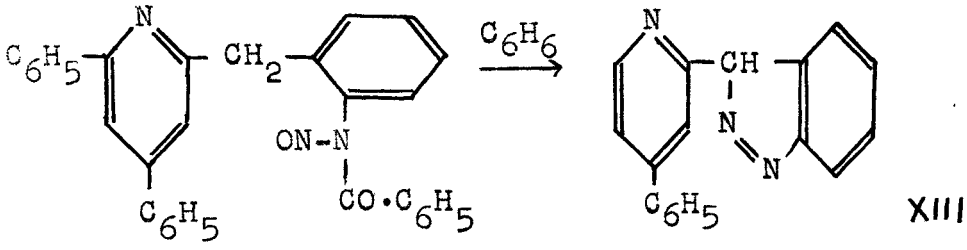
definite, pointed to the conclusion that the isomerisation product of the blue methyl-diphenyl-pyridine-imine was in fact a 2-amino-benzyl-4,6-diphenyl-pyridine. It now remained to establish the position of the amino group in the compound, i.e. in particular, whether the amino group was in O- or p- position and hence whether the intramolecular change was to be interpreted as an O- or p- benzidine change.

Jacobson and Huber (Ber. 41. 660/664 [1908]) had shown that the nitroso-compounds of o-benzoylamino- and p-benzoylamino-diphenyl methane can be distinguished by their behaviour on boiling in benzene. The former compound splits off benzoic acid and ring closure occurs with formation of a phenyl-indazole (a), whereas the latter loses benzoic acid and nitrogen giving rise to a diphenyl derivative (b).

(a) 

(b) 

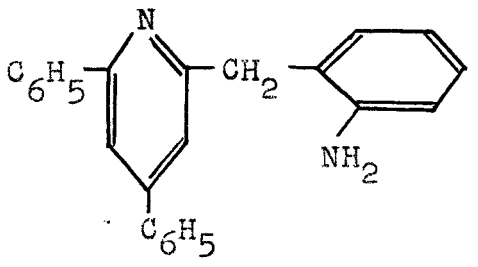
Schneider and Weiss therefore prepared the nitroso-benzoyl derivative of their isomerisation product and submitted it to the above reaction. They obtained, in small yield, a crystalline substance, whose nitrogen content was in agreement with the figures required for the indazole derivative (XIII). The reaction had therefore apparently gone as follows:-



XIII.

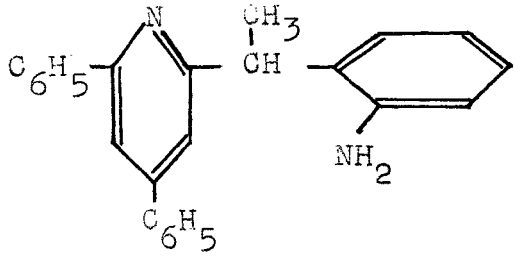
+ $C_6H_5 \cdot COOH$

It was therefore concluded that solutions of 2-methyl-4,6-diphenyl-pyridine-N-phenylimine undergo an intramolecular change with the formation of the isomeric 2-(o-amino-benzyl)-4,6-diphenyl-pyridine (XIV).



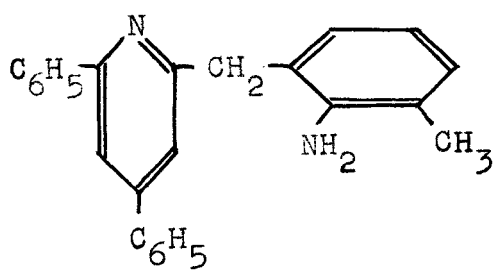
XIV.

Schneider and Weiss found, in addition, that the isomerisation product of the 2-ethyl-4,6-diphenyl-pyridine-N-phenylimine (VIII) investigated by Trebitz behaved analogously to that of the base (III). In particular its nitroso-benzoyl derivative again gave rise to an indazole on subjecting it to the reaction of Jacobsen and Huber. Hence the colourless base isolated by Trebitz (IX) must now be regarded as α-(o-amino-phenyl)-2-ethyl-4,6-diphenyl-pyridine (XV),

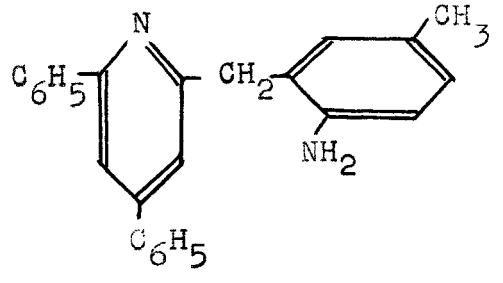


XV.

while the colourless bases of Görner, from the pyridine-imines (X) and (XI) are 2-(3'-methyl-2'-amino-benzyl) and 2-(5'-methyl-2'-amino-benzyl)-4,6-diphenyl-pyridine (XVI) and (XVII) respectively

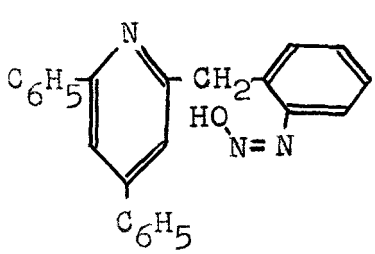
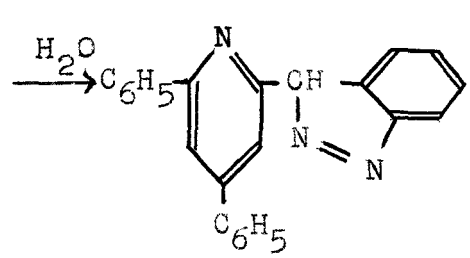


XVI.



XVII.

It has been mentioned that Schneider and Weiss, on attempting to remove the amino-group from 2-(o-amino-benzyl)-4,6-diphenyl-pyridine by diazotising and boiling with alcohol, obtained a crystalline compound, which they were unable to identify. Schneider accordingly omitted all reference to this experiment in publishing the results of the research (Berichte. 61, II. 2445, [1928]). It now seemed desirable to clarify this point, more particularly since the evidence leading to the establishing of the above formula for the isomerisation product is not absolutely conclusive. The author accordingly repeated the work of Weiss and found that his compound ($C_{20}H_{15}N_3$) was not absolutely pure. Recrystallisation from a better medium (toluene) gave beautiful colourless needles, m.p. 245°. Analysis results pointed to a formula $C_{24}H_{17}N_3$, i.e. a loss of three hydrogen atoms and a gain of one nitrogen atom, compared with the original substance, $C_{24}H_{20}N_2$. It was therefore concluded that the substance was 2-(3'-indazolo)-4,6-diphenyl-pyridine (XVIII), formed by ring closure with elimination of water from the intermediate diazonium compound.

XIV. $\xrightarrow{O=N\cdot OH}$  $\xrightarrow{H_2O}$ 

XVIII.

Hence, by means of this simple experiment, it has now been definitely established that the amino-group is in the o-position and that the formula XIV ascribed to the isomerisation product of 2-methyl-4,6-diphenyl-pyridine-N-phenylimine is, in fact, correct.

It should at this stage be pointed out that the intramolecular change so far discussed was discovered more than ten years ago. During that period Professor Schneider had come to doubt whether his interpretation of the reaction was entirely correct. The indentification of the above compound as an indazole derivative was however entirely conclusive and, moreover, the method employed was now found to correspond to a general method for preparing such substances (c.f. Berichte. 37, 2556). The way was accordingly now open for a more exhaustive examination of this intramolecular change, based on more modern ideas now being applied to such phenomena and, in particular, on recent developments of the electronic theory of valency as outlined by Arnt and Eistert [c.f. Tautomerie und Mesomerie, von Bernd Eistert - Sammlung chemischer und chemisch-technischer Vorträge - Neue Folge, Heft 40, 1938].

The remainder of this theoretical discussion is therefore concerned with the mechanism of this intramolecular change. In order that the picture presented may be as clear as possible, the author intends to proceed on the following lines:-

(A) Brief mention will be made of the distinction now drawn between tautomerism and mesomerism on the basis of the electronic theory.

(B) It will be shown how the intense colour of these anhydro-bases is explained by the large number of possible mesomeric states of which the compounds are capable.

(C) It is hoped to illustrate how the two formulæ (II and III) for these anhydro-bases are simply bounding forms of a common electron formula, the one being protomeric with it and the other electromeric, and how, further, the mechanism of the intramolecular change discussed above can be developed from the common 'zwitterion' formula.

(D) That this interpretation of the mechanism of the reaction can readily be verified by experiments involving the measurement of the velocity of the intramolecular change by the colour change which

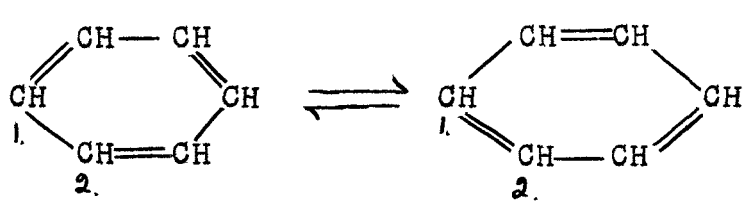
occurs, firstly with the original anhydro-base and subsequently with substituted anhydro-bases.

(E) It will then be shown how, having established the mechanism of the reaction, we have here a possible method of determining the effects of substitution by means of the velocity of decolourisation of substituted pyridine-aryl-imines.

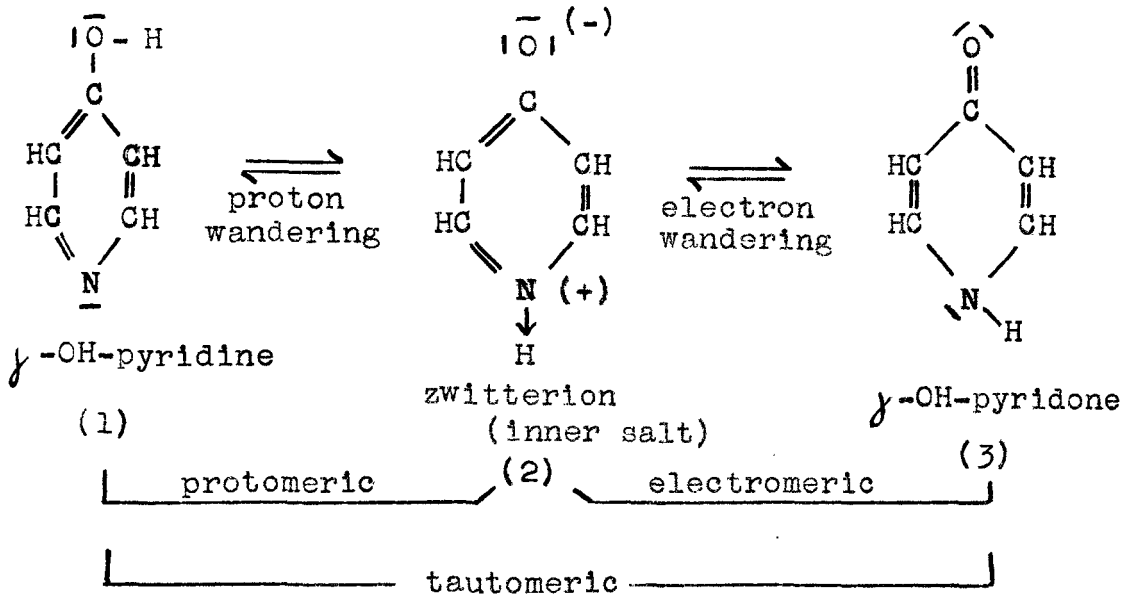
(A) The expression tautomerism was originally employed to describe the experimental observation that many compounds behave chemically as if constituted according to two different formulae. This included such changes as the equilibrium between keto-enol forms and also oscillation of valency phenomena, as in benzene, etc. In recent years, the term tautomerism has been modified to include only the former equilibria between structural isomers, while for the latter the term mesomerism is now used.

Tautomerism. $R\text{-}\underset{\underset{O}{\|}}{C}\text{-}CH_2\text{-}COOEt \rightleftharpoons R\text{-}C{=}CH\text{-}\underset{\underset{OH}{|}}{COOEt}$

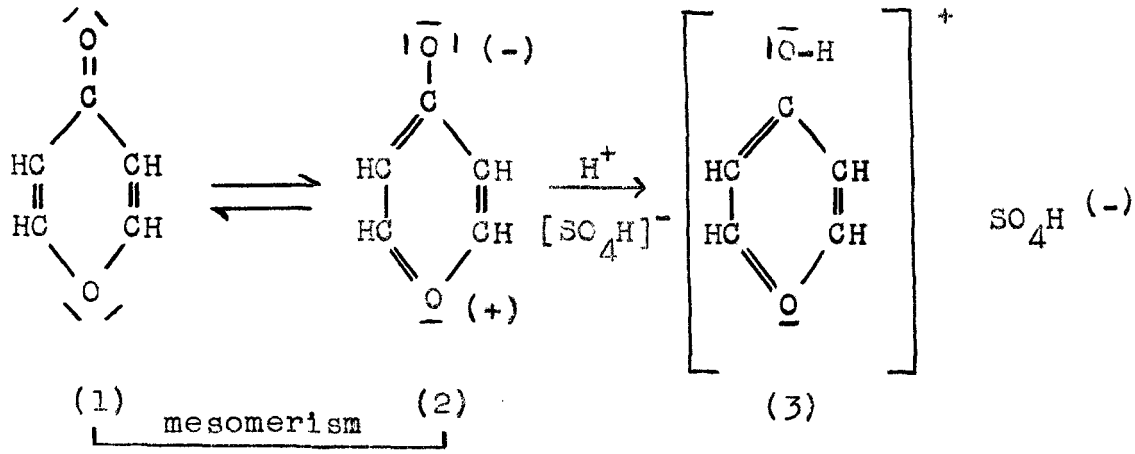
Mesomerism.



The difference between the two is well illustrated by the following examples, where - represents a lone pair of electrons.

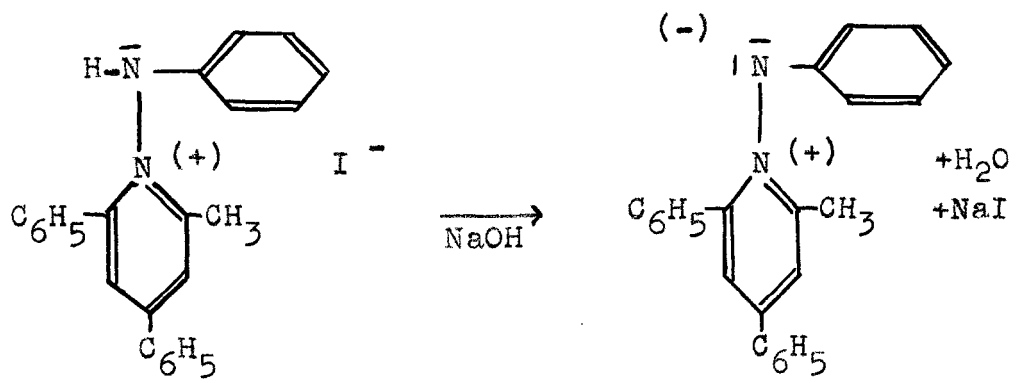


(1) and (3) are bounding forms, fixed by the hydrogen and both can be fetched out of the equilibrium. Tautomerism consists essentially of proton movement, followed by electron wandering and readjustment or oscillation of valences. If, however, proton wandering is excluded, but simply electron wandering and oscillation of valencies occurs, then we have mesomerism. The gamma pyrones may be cited as an example of mesomerism. Here, proton movement cannot occur.



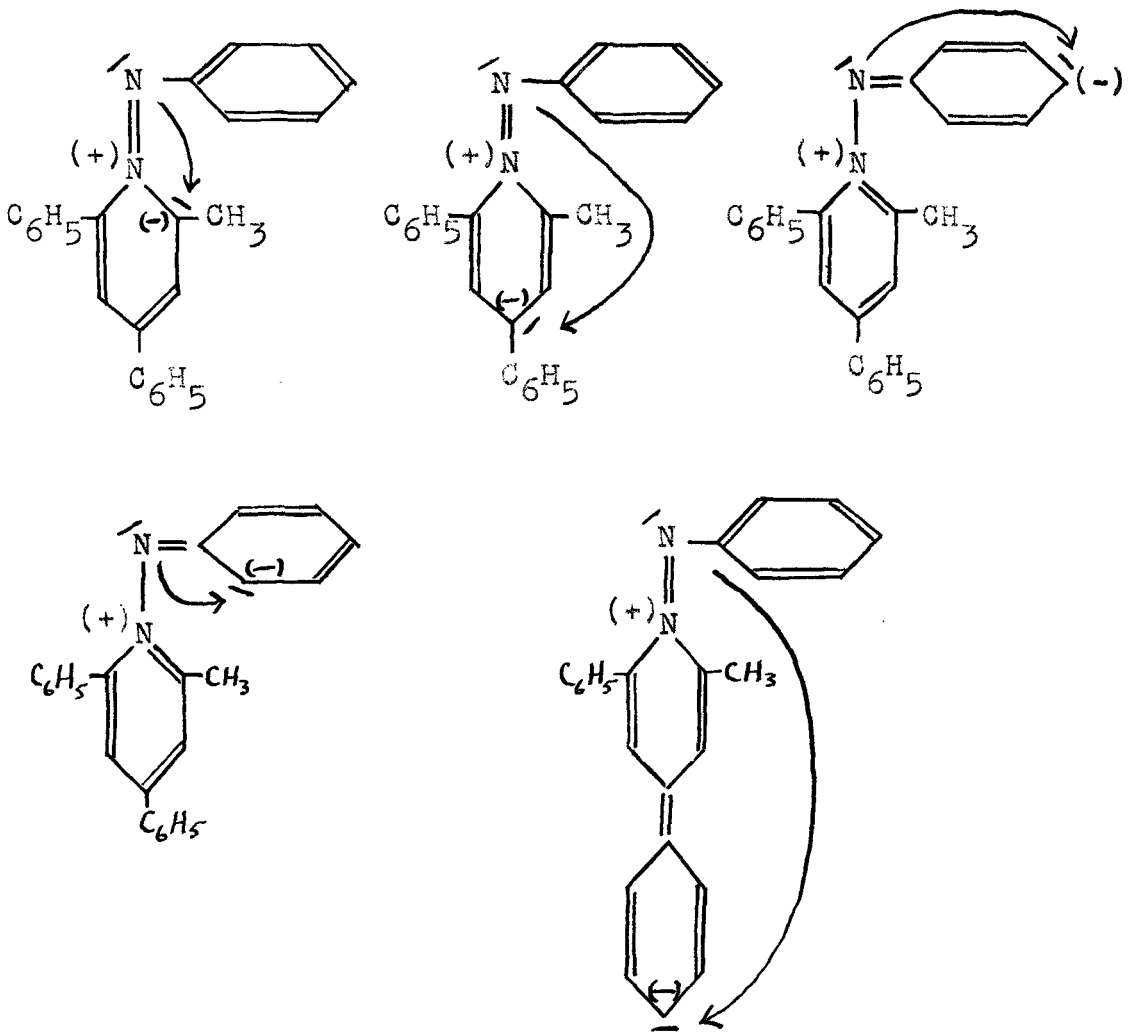
For instance, this substance gives a colourless salt with sulphuric acid. This is not in agreement with formula (1), since substances of this type (e.g. di-benzal-acetone) give intensely coloured solutions with sulphuric acid. This colourless salt must therefore be derived from the mesomeric formula (2) and has the constitution shown (3).

(B) Let us now examine the formation of the anhydro-base, 2-methyl-4,6-diphenyl-pyridine-N-phenylimine, from the point of view of the electronic theory.



I. XIX.

The hydrogen of the imino-group is removed as a proton, leaving a second lone electron pair on the nitrogen, which therefore now carried a negative charge. The resulting electron formula (XIX) for the anhydro-base may be called an ammonium azeniate. This substance will be capable of intense mesomeric states, due to electron wandering giving ammonium carbeniate forms. Some of these are indicated below:-

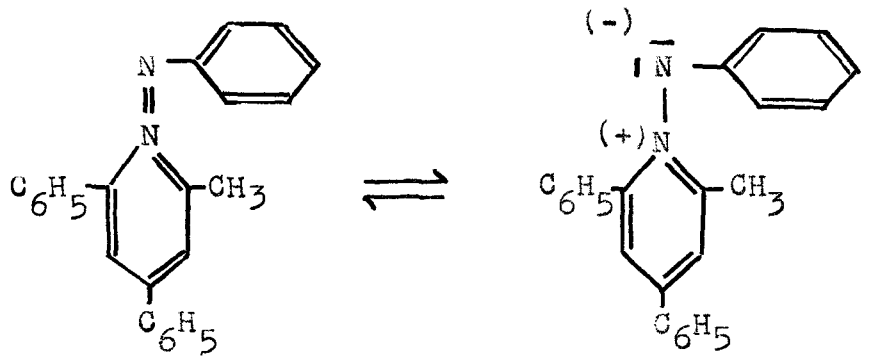


These mesomeric formulæ contain groupings normally regarded as chromophoric and satisfactorily explain the intense colour of the anhydrobase. A brief consideration of the physical basis of colour in organic substances leads to the same conclusion. Colour is simply the property of adsorbing light of a certain spectrum range. When electromagnetic rays meet a material particle they can be adsorbed. Since for atoms and molecules quantum laws hold, each chemical individual will adsorb from the complete spectrum only such characteristic bands as relate to the possibilities of excitement of the molecule (Anregungsmöglichkeiten). If E_1 and E_2 represent two possible states of energy of the molecule, then the energy of excitement $E = E_1 - E_2 = hj$, where h is Planck's constant and j the adsorbed frequency. The particle adsorbing the energy simply acts as a transformer of the energy streaming in. In the wave-length band up to about 2,000mu, adsorbtion is due almost entirely to electron excitement (Elektronen-anregung). From the above equation it follows that the adsorbed frequency is proportional to the required energy of excitement. Hence adsorbtion of the relatively long waves of the visible spectrum will be caused by such electrons as require comparatively slight energy of excitement. The

electrons of the so-called chromophoric groupings require the least energy to excite them and these are the cause of the chromophoric nature of such unsaturated compounds. Now the bounding formulæ of mesomerism simply give the outer range of the possible arrangements of these electrons and the more such bounding formulae which can be constructed, the greater will be the number of different possible quantum states which they include. We see, too, that the energy levels of the possible individual states of excitement must lie closer to each other the more of such energy levels we have. Hence, in such cases E will be very small and adsorbtion of small frequencies, i.e. long wave-lengths, will occur. Similarly, the intense colour of the pyridine-aryl-imines can be explained by the large number of possible mesomeric states which they are capable of assuming.

(C). It has been shown how N-phenylamino-2-methyl-4,6-diphenyl-pyridinium iodide (I) gives a deep violet anhydrobase on treatment with alkali, to which two possible formulæ (II and III) can be ascribed, the latter form representing a pyridine-arylimine while the former has the tautomeric methylene dihydro-pyridine structure. The pyridine-aryl-imine form (III) possesses the novel

grouping $\equiv N\ =N-$, not consistent with the electronic theory, the only possible analogies being the amino-oxides, $R_3N{=}O$ and the phosphine phenylimines of Staudinger, $R_3P{=}N{-}C_6H_5$. A little consideration will show, however, that the electronic formula (XIX) of the anhydrobase arrived at under (B) above represents 2-methyl-4,6-diphenyl-pyridine-N-phenylimine, (XIX) being simply the modern way of writing the more classical valency formula (III).

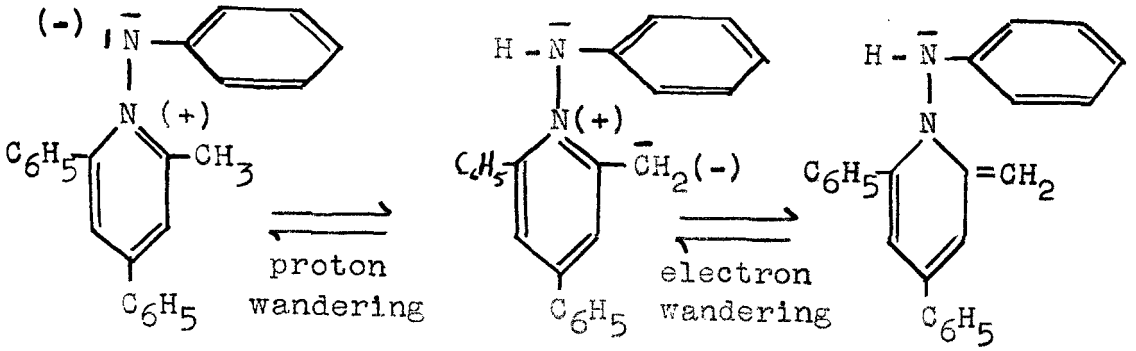


III. XIX.

classical valency formula. modern electronic formula.

We have seen further that this anhydrobase undergoes an intramolecular change in solution and that this conversion could readily be explained if we considered the substance as reacting in its tautomeric methylene dihydro-pyridine form. Let us now formulate the tautomerism of this compound as under (A) above, remembering that the first stage must be proton

wandering, followed by electron wandering and re-adjustment of valencies.

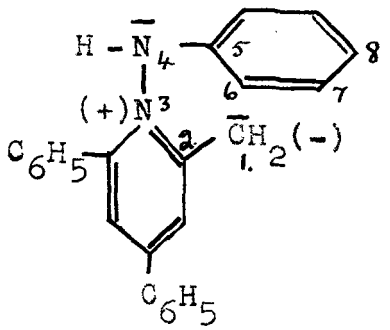


III or XIX XX II

We see, therefore, that II and III, the methylene dihydro-pyridine and pyridine-aryl-imine forms, respectively, are simply bounding forms of a common electron formula (XX), formula (III) being protomeric with it and formula (II) electromeric.

Now, the intramolecular change which the anhydrobase undergoes has already been formulated according to the classical theory of valency from the methylene dihydro-pyridine form (II). We are concerned here, however, with the mechanism of this intramolecular change on the basis of the modern electronic theory. Obviously, therefore, the mechanism of this change must be derived from the 'zwitterion' formula (XX). Let us rewrite this in a manner which

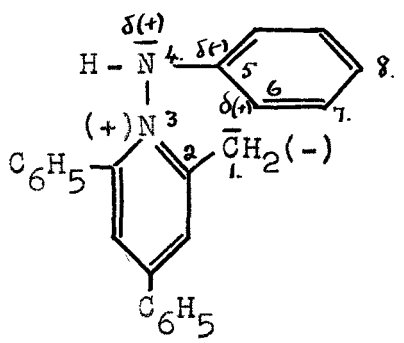
approximates more closely to the actual spacial configuration of the molecule.



For convenience, certain positions in the molecule have been numbered as shown. In this form, it at once becomes obvious why we have here a change similar to the o-benzidine change, linkage occurring between carbon atoms 1 and 6, and not between atoms 1 and 8. Further, the mechanism of the conversion involves linkage of carbon atoms 1 and 6 and rupture of the N-N linkage in positions 3 and 4.

Since the 1,6 positions are in such close proximity to each other, the electro-negative carbeniate group $-\bar{C}H_2(-)$ in position 1 will exert an electron pressure on the octet of carbon atom 6, tending to repel or displace the electrons of this octet towards positions 5 and 7. That is, position 6 will lose a certain increment of its normal electronic state, thus becoming more positive than before.

Hence, a small positive charge $\delta(+)$ has been induced at carbon atom 6 by the presence of the neighbouring electronegative charge in position 1. This does not confine itself to carbon atom 6 but spreads to neighbouring atoms which become alternately more positive or more negative (alternating stable and unstable octet). Similarly, this induction will be reinforced from the other side by the positive charge on nitrogen atom 3, which will exert an electron drag on nitrogen atom 4, thus inducing a $\delta(+)$ charge. It will be seen, therefore, that the molecule is in a somewhat unstable electronic state, and this may be illustrated diagramatically by the figure below:-



The intramolecular change which occurs in solution is a direct result of this electronic instability and on the principle that like charges repel and unlike charges attract, there will be attraction between carbon atoms 1 and 6 and repulsion in positions 3 and 4. Hence, in the limiting state, an intramolecular change will take

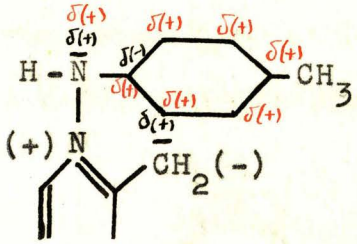
place to a system of greater stability, linkage occurring between positions 1 and 6 with rupture of the N-N bond in positions 3 and 4.

(D). The above interpretation of the mechanism of the intramolecular change can readily be verified by experiment. Since the anhydrobase is intensely violet and the isomeric product colourless, the velocity of the reaction can be measured by the colour change involved. Thus, if an alcoholic solution of the anhydrobase is heated, the violet colour gradually disappears and the solution becomes lightish-red in colour. In conducting such experiments, the following procedure was rigidly adhered to:-

1/2000 Mol. of the pyridinium iodide was placed in a 50cc. round-bottom flask, fitted with a reflux condenser and a small inlet tube. The flask was warmed gently with a small flame under a copper gauge, care being taken not to melt the solid iodide. On an adjacent wire gauge a small conical flask containing 20cc. absolute alcohol and 1cc. 2N. sodium hydroxide solution was heated to boiling and this hot solution quickly poured into the round-bottom flask containing the pyridinium iodide. The flame under the flask was momentarily raised till the alcoholic solution was again boiling, which usually occurred within ten seconds of

introducing the solution. Then the flame was lowered to such dimensions as to keep the solution refluxing gently. A stop-watch was started at the moment the alkaline alcoholic solution was added, that is, simultaneously with the appearance of the violet colour caused by the liberation of the anhydrobase, and was stopped only when the last trace of violet had disappeared from the solution. The experiment was conducted at a large window in bright daylight and the end-point was easily determinable. Thus, when N-phenylamino-2-methyl-4,6-diphenylpyridinium iodide (I) was treated in this way, the liberated 2-methyl-4,6-diphenylpyridine-N-phenylimine was found to lose its violet colour in 32 minutes.

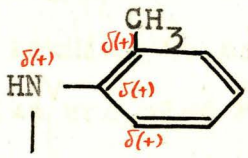
Now, supposing we consider the case of 2-methyl-4,6-diphenylpyridine-N-p-tolylimine.



The methyl group has a general $\delta(+)$ effect, shown in red, and this effect must reinforce the induced positive charges in positions 4 and 6. Hence, if the mechanism of the reaction is correct, the presence of the methyl group should further increase the instability of

the molecule by facilitating union between the 1,6 position and rupture of the 3,4 bond. In other words, the intramolecular change should proceed more rapidly than with the unsubstituted anhydrobase.

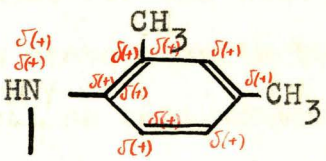
Similarly, in the case of 2-methyl-4,6-diphenylpyridine-N-o-tolylimine the ortho-methyl group will have a similar effect



and the reaction should proceed more rapidly.

Measurement of the actual times required gave 7·85 minutes for the p-compound and 7·75 minutes for the o-compound.

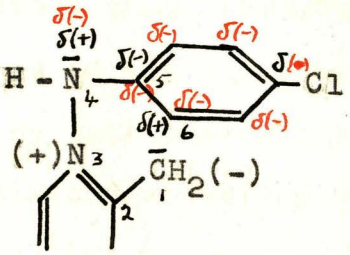
Moreover, when both methyl groups are present, as in 2-methyl-4,6-diphenylpyridine-N-2',4'-xylylimine



the δ(+) effects of the two methyl groups should reinforce each other and the reaction should go even more rapidly than for the tolyl compounds.

Measurement of the time required in this case gave 2·18 minutes.

Supposing, however, we introduce an electronegative constituent such as chlorine in the para position.

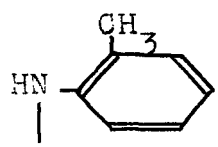


Here, the general effect is $\delta(-)$, opposing the electron pressure tending to make the octet of carbon atom 6 more positive and also opposing the electron drag on the nitrogen of the imino-group. The result should therefore be to stabilise the molecule by rendering union between atoms 1 and 6 and rupture of the 3,4 bond more difficult. Hence, the intramolecular change should take longer in this case than with the unsubstituted compound.

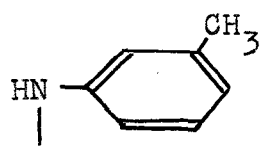
Measurement of the velocity of the intramolecular change of 2-methyl-4,6-diphenylpyridine-N-p-chlorophenylimine gave 95 minutes for the time required.

From the above results it can be seen that, assuming the general or nett effect of the methyl group to be $\delta(+)$ and that of the chlorine atom to be $\delta(-)$, an assumption which is now generally acceptable, the interpretation of the mechanism of the intramolecular change undergone by the pyridine-arylimines developed in (C) above has been verified by experiment.

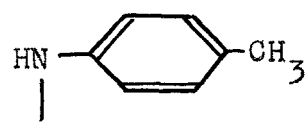
(E). This intramolecular change would appear to afford a novel method of determining the effects of substitution, since these effects can be directly measured in terms of the velocity of the intramolecular change, simply by introducing the desired atom or group into the molecule and measuring the time required for decolorisation. Let us consider, for example, the substitution of a methyl group in o-, m- and p- positions. These three compounds may be represented diagrammatically by (a), (b) and (c) respectively, as shown below, the pyridine part of the molecule being the same in every case.



(a)



(b)

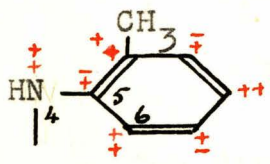


(c)

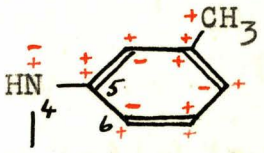
The times measured for the intramolecular change in these three cases are given below, the acceleration caused by the introduction of the methyl group being calculated by dividing 32 minutes by the measured time in each instance.

Substituent.	Time.	Acceleration.
2-methyl (a)	7·75 minutes	4·13
3-methyl (b)	25·5 minutes	1·26
4-methyl (c)	7·85 minutes	4·08

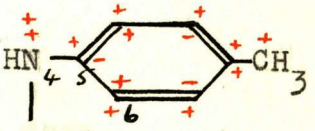
Substitution in positions 2 and 4 has therefore a like effect, whereas a methyl group in position 3 causes only a slight acceleration. From this, it is apparent that the effect of the methyl radical is not simply a field effect, otherwise the effect of m- substitution would be intermediate between the other two. There must be two different effects working and of these one must be an alternating effect, alternatively opposing and reinforcing the other as illustrated below.



(a)



(b)



(c)

We thus have two effects, a direct effect, which may be called the D effect, and an alternating effect, the A effect. In (a) and (c) these reinforce each other in positions 4 and 6, whereas in (b) they

act in opposition to each other. Further, of these two effects, the D effect is the greater, since the sum effect in (b) causes acceleration and must therefore be $\delta(+)$. Hence, taking the mean acceleration of (a) and (c), we can write

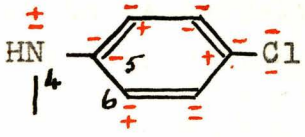
$$D + A = 4{\cdot}105$$

and $$D - A = 1{\cdot}26$$

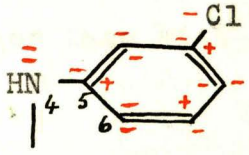
from which we get $$D = 1{\cdot}89 \text{ A.}$$

That is, the direct effect is almost twice as great as the alternating effect.

Let us now consider the effect of an electronegative group, such as chlorine, in meta- and para-positions.



(d)



(e)

The direct effect is $\delta(-)$ in this case. Moreover, the alternating effect will oppose the direct effect in positions 4 and 6 in (d) but will reinforce it in (e). We saw that the p-chloro-compound took 95 minutes to decolorise, so that here again the direct effect is the greater. Moreover, from (e) we see that

the meta-compound should take even longer to lose its colour than the p-compound. This was borne out by experiment

Substituent.	Time.	Retardation.
p-chlorine (d)	95 minutes	2·97
m-chlorine (e)	370 minutes	11·56

Therefore again we can write

$$D - A = 2{\cdot}97$$

and $$D + A = 11{\cdot}56$$

giving $$D = 1{\cdot}69\ A.$$

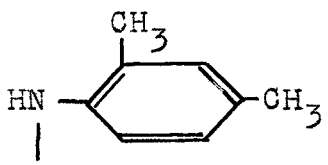
That is, in the case of chlorine, the alternating effect is relatively stronger than with the methyl group.

Further, we can compare the absolute effect of the chlorine atom and the methyl group by comparing their influence on the velocity of the reaction. For this we must take the maximum effects in each case, that is, when D and A effects are working together, in other words we must compare p-methyl (c) with m-chlorine (e).

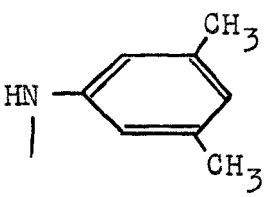
Substituent.	Time.	Acceleration.
4-methyl (c)	7·85 minutes	+ 4·08
3-chlorine (e)	370 minutes	-11·56

Therefore the chlorine atom has an effect 2·83 times that of the methyl group, but in the opposite sense.

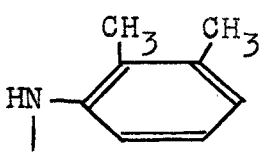
Let us now consider the effect of introducing two methyl groups. The following compounds have been studied:-



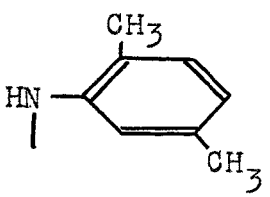
(f)



(g)



(h)



(i)

The times measured for these compounds are given in the following table:-

Substituent.	Time.	Acceleration.
2,4-dimethyl (f)	2·18 minutes	14·7
3,5-dimethyl (g)	19 minutes	1·68
2,3-dimethyl (h)	4 minutes	8
2,5-dimethyl (i)	5 minutes	6·4

Since, in the case of substituents such as 2,4-dimethyl the reaction was completed in such a short space of time, a fairly large error was involved in the measurement of the intramolecular change. Thus the error incurred at the beginning before the solution started to boil again and the slight error always incurred in recording the exact end-point amounted to quite a considerable percentage error in such a case where the intramolecular change only occupied some two minutes. It was accordingly deemed advisable to carry out the reaction in methyl alcohol, which has a lower boiling point than ethyl alcohol, thus giving correspondingly longer times for the intramolecular change. The following table indicates the results given by some of these compounds in methyl alcohol.

Intramolecular change in methyl alcohol.

Substituent.	Time.	Acceleration.
none	123·5 minutes	-
2-methyl (a)	30·5 minutes	4·05
3-methyl (b)	99·5 minutes	1·24
2,4-dimethyl (f)	7·56 minutes	16·32
3,5-dimethyl (g)	77·5 minutes	1·59
2,3-dimethyl (h)	15·33 minutes	8·04
2,5-dimethyl (i)	19·75 minutes	6·25

From the above two tables, several interesting relations emerge. For instance, if we denote the acceleration caused by an ortho- or para- methyl group by x and that caused by a meta- methyl group by y, we have the following:-

Substituent.	Acceleration.
2-methyl	x
3-methyl	y
2,4-dimethyl	x^2
3,5-dimethyl	y^2

That is, if the methyl groups are in meta- position to each other, or, in other words, if their mutual D and A effects reinforce each other, then the resultant effect is the product of the effect of each methyl group separately.

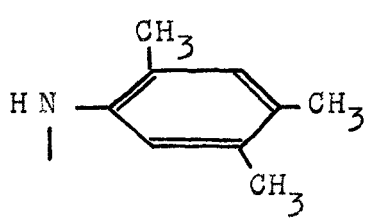
When, however, the two methyl groups are in ortho- or para- position to each other and their mutual A and D effects are in opposition, as in the 2,3- and 2,5-dimethyl-derivatives, then this does not hold.

Substituent.	Acceleration.	Product (xy).
2,3-dimethyl (h)	8·05	5·02
2,5-dimethyl (i)	6·25	5·02

The actual effect is greater than the product of the two separate effects in both cases, being much larger when the two methyl groups are in o- position and slightly larger when they are in p- position.

A similar result was obtained on substituting three methyl groups, as in the compound (j).

(j)



This decolorised in 1·3 minutes in ethyl alcohol and in 4·8 minutes in methyl alcohol, giving an acceleration factor 25·7 compared with the calculated value of 20·3 for x^2y.

This additional $\delta(+)$ effect of two or more methyl groups in o- or p- positions to each other must be due to the mutual effect they exert on each other.

In addition to the compounds discussed above, bromine and iodine were also introduced into the p-position. The table below gives the values obtained in these cases, the corresponding p-chloro-compound being included for purposes of comparison.

Substituent.	Time.	Retardation.
p-chlorine	95 minutes	2·97
p-bromine	152 minutes	4·75
p-iodine	175 minutes	5·47

These results are as expected and illustrate the increasing retardation caused by the increase in electronegative character of the substituting group.

Summing up, it would appear that in considering the effects of substitution on the pyridine-arylimines at least two effects must be taken into account. One of these is a direct effect and the other an alternating effect, the former being the larger in all the cases studied. In the case of the methyl group, these experiments have shown that the direct effect, or D effect, as it has been called, does not appear to be a field effect, but must rather be regarded as an electromeric effect, occurring not through space but through the carbon chain. Otherwise an o-methyl should have a much greater $\delta(+)$ effect than a p-methyl group. The methyl group would, in fact, appeat to have an almost negligible field effect. In addition to this direct effect there is an alternating effect, the methyl group functioning here as an electronegative group. The resultant of these two effects is always $\delta(+)$ since the electromeric effect is the greater.

In the case of chlorine as substituent, the direct effect is again to be regarded as an electromeric effect. The field effect of chlorine only appears to come into full play in the ortho- position. Substitution of o-chlorine was expected to retard the reaction to an even greater extent than p- substitution. It was found, however, to have exactly the opposite

effect as was shown by the fact that the intramolecular change took only 36 minutes, that is, almost the same as the time taken by the unsubstituted compound (32 minutes). Thus in some way the field effect of the chlorine has almost neutralised the resultant of the other two effects tending to retardation. This it can only have done by influencing the charge of the quaternary nitrogen atom and altering the electronic equilibrium of the molecule.

In addition to the effect which the introduction of substituents has on the velocity of the intramolecular change, it should be evident that it will also have an effect on the mesomerism of the compound, as illustrated in (B) above. Since the mesomerism is responsible for the intense colour of these anhydrobases, anything which influences the mesomerism must also influence the colour. Hence the colour of the substituted anhydrobases will differ according to the nature of the substituting groups and, since the electronic nature of the substituents is again the decisive factor, there should be an analogy between the relative colour of the anhydrobases and the velocity of the intramolecular change which they undergo. That there is such an analogy is evident from tables IV and V.

These give the colour of the anhydrobases and the times required for the intramolecular change in ethyl and methyl alcohol respectively. It will be seen that as the colour of the anhydrobases passes from violet to blue, the velocity of the intramolecular change increases, while, as the colour passes from violet up to red the velocity of the intramolecular change decreases. That is, the bluer the solution of the anhydrobase in alcohol, the shorter is the time required for the intramolecular change, the redder the solution, the longer the time required. The only exception to this rule was the o-chloro-compound, which, while taking up its proper place in the colour series, fell completely out of line in the time series, as has already been mentioned. This affords an excellent illustration of the correctness of the distinction now drawn between mesomerism and tautomerism on the basis of the electronic theory. The mesomerism of the anhydrobase is responsible for the colour, whereas the mechanism of the intramolecular change is derived from the tautomerism of the compound. The field effect of the chlorine does not appear to influence the mesomerism but does influence the tautomeric zwitterion from which the intramolecular change occurs.

TABLE IV

Colour and velocity of intramolecular change in ethyl alcohol.

Substituent.	Time.	Colour.
2,4,5-trimethyl	1·3 minutes	pure blue
2,4-dimethyl	2·18 minutes	corn-flower blue
2,3-dimethyl	4 minutes	indigo-blue
2,5-dimethyl	5 minutes	indigo-blue
2-methyl	7·75 minutes	ultramarine-blue
4-methyl	7·85 minutes	ultramarine-blue
3,5-dimethyl	19 minutes	violet-blue
3-methyl	25·5 minutes	blue-violet
none	32 minutes	violet
p-chlorine	95 minutes	red-tinged violet
p-bromine	152 minutes	red-violet
p-iodine	175 minutes	red-violet
o-chlorine	36 minutes	violet-red
m-chlorine	370 minutes	violet-tinged red

TABLE V

Colour and velocity of intramolecular change in methyl alcohol.

Substituent.	Time.	Colour.
2,4,5-trimethyl	4·8 minutes	blue
2,4-dimethyl	7·56 minutes	ultramarine-blue
2,3-dimethyl	15·33 minutes	violet-tinged blue
2,5-dimethyl	19·75 minutes	violet-tinged blue
2-methyl	30·5 minutes	blue-violet
4-methyl	32·33 minutes	blue-violet
3,5-dimethyl	77·5 minutes	blue-tinged violet
3-methyl	99·5 minutes	violet
none	123·5 minutes	red-violet
p-chlorine	-	violet-tinged red
p-bromine	-	violet-tinged wine-red
p-iodine	-	violet-tinged wine-red
o-chlorine	-	wine-red
m-chlorine	-	carmine-red

B. EXPERIMENTAL.

2-Methyl-4,6-diphenyl-pyrylium sulphoacetate.

c.f. Schneider and Seebach, Ber. 54, 2289.

100cc. acetic anhydride and 30cc. concentrated sulphuric acid were slowly mixed with thorough cooling. When the evolution of heat had ceased the mixture was transferred in a flask to a waterbath warmed to 75-80°, the temperature of the bath being controlled by means of a thermometer. After 2-3 hours, during which the temperature was not allowed to exceed 80°, no free sulphuric acid remained in the liquid (barium chloride test).

The contents of the flask were then cooled to room temperature and 30cc. acetophenone added. The mixture was warmed gently at 45-50° on a waterbath for about 34 hours. The previously reddish-brown mixture began to turn dark brown after about one hour. After some hours heating a further 10-20cc. of acetophonone were added. At the end of the stated time, an equal volume of alcohol was added. The cooled reaction mixture was seeded with a few crystals obtained from a small sample by careful addition of ether and scratching with a glass rod, whereupon the sulphoacetate fell out in such quantity that the liquid solidified

to a thick paste. The crystals were filtered off and washed with alcohol containing a little ether. From the mother-liquid a further small amount was obtained by careful addition of ether. The total yield of crude product was about 50% of the theoretical. The salt was purified by recrystallisation from hot water. It formed fine yellow needles, m.p. 204°. It was fairly insoluble in water but underwent gradual decomposition by hydrolysis, especially on warming, yielding pyranhydrone, which was evident from the blue colouration. In acidified water, however, it could be dissolved easily without decomposition. Such solutions were almost colourless but showed an intense blue fluorescence.

2-Methyl-4,6-diphenyl-pyrylium iodide.

The iodide was characterised by the beautiful red colour of its crystals. It was obtained, on cooling, from an acid solution of the sulphoacetate treated with a concentrated potassium iodide solution at 80°. On slow cooling it crystallised in long needles, m.p. 222°. It could be recrystallised only from slightly acid solution, but decomposed on heating in neutral solution.

N-Phenylamino-2-methyl-4,6-diphenyl-pyridinium iodide.

The pyrylium iodide above was suspended in boiling benzene and a solution of phenylhydrazine in benzene gradually added drop by drop. After a short time the red iodide was decomposed and replaced by fine crystals of a yellow salt. The new iodide was recrystallised from alcohol and melted at 200°. It was only slightly soluble in water but imparted a definite yellow colour to it. It decomposed fairly rapidly on exposure to light, becoming dark brown in the process.

Intramolecular Change of N-phenylamino-2-methyl-4,6-diphenyl-pyridinium iodide. Formation of 2,-(o-aminobenzyl)-4,6-diphenyl pyridine.

10g. of 2-methyl-4,6-diphenyl-pyridinium iodide were dissolved in 250cc. boiling alcohol. 2cc. of 7% caustic soda solution were added and the mixture boiled for ten minutes under reflux, when the deep violet colouration first produced had disappeared. Boiling was continued and a further four similar amounts of caustic soda solution added at intervals of 15 minutes. When the violet colour had disappeared for the last time, a little zinc dust was added and the contents of the flask heated till the solution was light yellow in colour. The liquid was then filtered hot from the

residual zinc, washed with hot alcohol and the alcohol partly driven off by steam-distillation. On cooling, yellowish-brown crystals were precipitated. After several recrystallisations from alcohol, these were obtained as colourless rhombic needles, m.p. 144°. The yield of crude product was about 50%.

Colour of anhydrobase.

(a)	In ethyl alcohol	violet.
(b)	In methyl alcohol	red-violet.

Measurement of velocity of intramolecular change.

1/2,000 Mol. (0·2320g.) N-phenylamino-2-methyl-4,6-diphenyl-pyridinium iodide in 20cc. alcohol + 1cc. 2N. NaOH.

(a)	Time in ethyl alcohol	32	minutes.
(b)	Time in methyl alcohol	123·5	minutes.

Formation of an indazole derivative, 2-(3'-indazolo)-4,6-diphenyl-pyridine.

(a) Attempted removal of the amino-group. Decompostion of the diazotised base with alcohol. (c.f. Griess, Annalen, 137, 69. [1866])

1g. 2-(o-aminobenzyl)-4,6-diphenyl pyridine was dissolved in 10cc. warm glacial acetic acid and 20cc.

dilute sulphuric acid (1:5) added. The solution was cooled in ice to below +5° and diazotised with 3cc. N. sodium nitrite. The diazotised solution was allowed to stand for a quarter of an hour at room temperature and was then poured into 50cc. alcohol at about 40°. The solution became reddish-brown in colour. The alcohol was distilled off in steam, when a reddish-brown crystalline precipitate was obtained on allowing to cool. This was filtered off and washed with water. Yield: 0·9g. (87% theoretical). m.p. 210°. After several recrystallisations from toluene, the compound was obtained as small colourless needles, m.p. 245°.

Analysis:- 4·912mg. gave 14·880mg. CO_2, 2·190mg. H_2O and 0·012mg. residue.

Found:- C. 82·62%, H. 4·99%.

Calc. for $C_{24}H_{17}N_3$:- C. 82·96%, H. 4·94%.

(b) Attempted preparation of a phenol derivative.

(c.f. Houben. 3, 60)

A solution of 1g. 2-(o-aminobenzyl)-4,6-diphenyl pyridine in 10cc. water and 1·5cc. concentrated sulphuric acid was gradually diazotised with a concentrated solution of 0·5g. sodium nitrite. On leaving the liquid to stand no evolution of nitrogen occurred, but the indazole derivative fell out as a yellow

amorphous powder. On filtering this off and recrystallising, the same product as before was obtained. Yield: 85% theoretical.

N-(ortho-Tolylamino)-2-methyl-4,6-diphenyl-pyridinium iodide.

3g. Pyrylium iodide were suspended in 60cc. of boiling benzene and a solution of 3g. o-tolyl-hydrazine in 30cc. benzene added from a dropping-funnel. The red iodide disappeared rapidly and a yellow crystalline precipitate formed. This was filtered, washed with benzene and dried. Yield: 3·3g. Recrystallisation from alcohol and subsequent drying in a vacuum desiccator gave yellow leaflets, m.p. 176°, which darkened rapidly on exposure to light.

Product of intramolecular conversion of N-(ortho-tolylamino)-2-methyl-4,6-diphenyl-pyridinium iodide. 2-(3'-Methyl-2'-aminobenzyl)-4,6-diphenyl pyridine.

The ortho-tolylamino-pyridinium iodide was dissolved in ten times its weight of alcohol by boiling on the waterbath and the calculated amount of caustic soda solution added in portions as before. The solution decolourised gradually. After the final addition of alkali and the disappearance of the violet-blue colour the solution was cleared to light yellow by

boiling with zinc dust and the product worked up as before. Yield: 50%. Colourless needles (from alcohol), m.p. 126°.

Colour of anhydrobase.

(a) In ethyl alcohol — ultramarine-blue.

(b) In methyl alcohol — blue-violet.

Measurement of velocity of intramolecular change.

1/2,000 Mol. (0·239g.) N-(ortho-tolylamino)-2-methyl-4,6-diphenyl-pyridinium iodide in 20cc. alcohol + 1cc. 2N. NaOH.

(a) Time in ethyl alcohol — 7·75 minutes.

(b) Time in methyl alcohol — 30·5 minutes.

N-(p-Tolyl-amino)-2-methyl-4,6-diphenyl-pyridinium iodide.

The reaction product from p-tolyl-hydrazine (3g.) and 2-methyl-4,6-diphenyl-pyrylium iodide (3g.) was obtained in the same manner as described above for N-(o-tolylamino)-2-methyl-4,6-diphenyl-pyridinium iodide. The pyrylium iodide was well powdered and the mixture boiled for about one hour in benzene. The yellow pyridinium iodide possessed similar properties to the above. Yield: 3·5g., m.p. 173°.

Conversion product of N-(p-tolylamino)-2-methyl-4,6-diphenyl-pyridinium iodide. 2-(5'-Methyl-2'-amino-benzyl)-4,6-diphenyl-pyridine.

On treatment with alkali in alcoholic solution an intramolecular change similar to that described above for the corresponding o-tolyl derivative occurred. The product was isolated as before. Colourless needles (from alcohol), m.p. 165°.

Colour of anhydrobase.

(a) In ethyl alcohol — ultramarine-blue.

(b) In methyl alcohol — blue-violet.

Measurement of velocity of intramolecular change.

1/2,000 Mol. (0·239g.) N-(p-tolylamino)-2-methyl-4,6-diphenyl-pyridinium iodide in 20cc. alcohol + 1cc. 2N. NaOH.

(a) Time in ethyl alcohol — 7·85 minutes.

(b) Time in methyl alcohol — 32·33 minutes.

N-(meta-Tolylamino)-2-methyl-4,6-diphenyl-pyridinium iodide.

8·5g. Pyrylium iodide were suspended in 50cc. boiling benzene and a solution of 5g. m-tolyl-hydrazine in the minimum quantity of benzene added slowly, drop by drop. The red iodide was quickly replaced by a yellow crystalline precipitate. The solution was

refluxed on the waterbath till the product was completely yellow in colour (about one hour). Weight of crude product: 10g., m.p. 178°. Several recrystallisations from alcohol yielded beautiful yellow needles, m.p. 187°.

Analysis:

Found:- C. 62·69%, H. 4·83%.

Calc. for $C_{25}H_{23}N_2I$:- C. 62·76%, H. 4·81%.

Intramolecular Conversion. Formation of 2-(4'-methyl-2'-aminobenzyl)-4,6-diphenyl-pyridine.

5g. N-(m-Tolylamino)-2-methyl-4,6-diphenyl-pyridinium iodide were dissolved in 125cc. boiling alcohol, and 10cc. 7% sodium hydroxide solution added. The resulting violet solution was heated to boiling for about one hour on the waterbath till the colour was only reddish-brown. The colour was further reduced to light yellow by the addition of a little zinc dust, the solution filtered hot and allowed to cool. After standing overnight, the yellowish-brown crystals which separated were filtered, washed with alcohol and dried. Weight: 2·0g., m.p. 156-158°. Recrystallisation from alcohol gave light yellow crystals, m.p. 161°. Further recrystallisations were necessary before the product was completely pure. Beautiful prisms, m.p. 168°.

Analysis:- 5·199mg. gave 16·270mg. CO_2 and 3·010mg. H_2O.

Found:- C. 85·7%, H. 6·29%.

Calc. for $C_{25}H_{22}N_2$:- C. 85·32%, H. 6·43%.

Colour of anhydrobase.

(a) In ethyl alcohol blue-violet.

(b) In methyl alcohol violet.

Measurement of velocity of intramolecular change.

1/2,000 Mol (0·239g.) N-(m-tolylamino)-2-methyl-4,6-diphenyl-pyridinium iodide in 20cc. alcohol + 1cc. 2N. NaOH.

(a) Time in ethyl alcohol 25·5 minutes.

(b) Time in methyl alcohol 99·5 minutes.

N-(2,4-Xylylamino)-2-methyl-4,6-diphenyl-pyridinium iodide.

(a) 2,4-di-Methyl-diazobenzene sodium sulphonate.

(c.f. Altschuh, Ber. 25, 1843)

17·5g. 1,3,4-Xylidine were dissolved in 150cc. water and 34cc. concentrated hydrochloric acid stirred in slowly. The finely divided hydrochloride thus formed was carefully diazotised with a solution of 11g. sodium nitrite in 80g. water and afterwards poured into a solution of 80g. crystalline sodium sulphite in 320g. water and 24g. 35% NaOH, cooled directly with 100g. ice. The diazosulphonic acid

salt was precipitated as sulphur-yellow crystals. These were filtered off and a further yield obtained by salting out from the filtrate. The precipitate was washed with salt solution and water and was then practically pure. Recrystallisation from a little water gave fine yellow leaflets. Yield: 30g.

(b) 2,4-di-Methyl-phenylhydrazine sodium sulphonate.

30g. of the above were dissolved in 165g. hot water, filtered hot and treated with 16·5g. glacial acetic acid. The solution was then decolourised by the gradual addition of about 16·5g. zinc dust, boiled for a few minutes and filtered. To the colourless filtrate 165cc. of saturated salt solution were added, thus bringing about a rapid cooling and preventing back-oxidation. On cooling, the precipitate was filtered, washed with alcohol and dried on a porous plate. Small colourless prisms. Yield: 21g.

(c) 2,4-di-Methyl-phenylhydrazine hydrochloride.

The sulphonate was decomposed with concentrated aqueous hydrochloric acid. From 21g. of the sodium sulphonate only 8·5g. of the hydrochloride were obtained. White prisms, m.p. 183°.

(d) 2,4-di-Methyl-phenylhydrazine.

8·5g. of the hydrochloride were warmed with 15cc. NaOH solution (1:3) on the waterbath till the salt was completely decomposed and the free hydrazine had separated as an oily layer. On quick cooling this solidified to crystal clusters which were powdered and washed with water and ether. White crystals were obtained, m.p. 86°. Weight, 5g.

(e) N-(2,4-Xylylamino)-2-methyl-4,6-diphenyl-pyridinium iodide.

11·5g. 2-Methyl-4,6-diphenyl-pyrylium iodide were suspended in about 100cc. boiling benzene and a solution of 5g. 2,4-xylylhydrazine in benzene added drop by drop. After half an hour the product was completely yellow in colour. After cooling, the new iodide was filtered, washed with benzene and dried. Yield: 14·6g. m.p. 142°. The substance was fairly pure but could not be recrystallised owing to decomposition. (see later).

Analysis:

Found:-	C.	62·8%,	H.	5·27%.
Calc. for $C_{26}H_{25}N_2I$:-	C.	63·42%,	H.	5·08%.

(f) Intramolecular change. Formation of 2-(3',5' dimethyl-2'-aminobenzyl)-4,6-diphenyl pyridine.

5g. of the above iodide were treated with a boiling mixture of 500cc. alcohol and 25cc. 2N. sodium hydroxide. After boiling for half an hour the solution was dark red in colour. It was cleared to light yellow as before by addition of some zinc dust, filtered while hot and allowed to cool. The product came down as beautiful long white needles, m.p. 164°. (1·3g.). After two recrystallisations from alcohol the substance had m.p. 166° and was completely pure.

Analysis:- 5·206mg. gave 16·325mg. CO_2 and 2·950mg. H_2O.

Found:- C. 85·52%, H. 6·34%.

Calc. for $C_{26}H_{24}N_2$:- C. 85·71%, H. 6·59%.

Colour of anhydrobase.

(a) In ethyl alcohol — corn-flower blue.

(b) In methyl alcohol — ultramarine blue.

Measurement of velocity of intramolecular change.

1/2,000 Mol. (0·246g.) N-(2,4-xylylamino)-2-methyl-4,6-diphenyl-pyridinium iodide in 20cc. alcohol + 1cc. 2N. NaOH.

(a) Time in ethyl alcohol — 2·18 minutes.

(b) Time in methyl alcohol — 7·56 minutes.

(g) Indazole derivative. 2-(5',7' di-methyl-3' indazolo)-4,6-diphenyl-pyridine.

0•5g. of the above product was dissolved in 5cc. hot glacial acetic acid and 10cc. sulphuric acid (1:5) added. The solution was well cooled and diazotised with 1•5cc. N sodium nitrite solution. After standing overnight the yellow crystals were filtered and washed with water. Yield: 0•5g. m.p. 218-220°. Three recrystallisations from toluol with addition of norit gave fine white needles. m.p. 258°.

Analysis:- 5•328mg. gave 16•260mg. CO_2 and 2•600mg. H_2O.

Found:- C. 83•23%, H. 5•46%.

Calc. for $C_{26}H_{21}N_3$:- C. 83•21%, H. 5•60%.

N-(2,3-Xylylamino)-2-methyl-4,6-diphenyl-pyridinium iodide.

(a) 2,3 di-Methyl-diazobenzene sodium sulphonate.

5g. ortho-xylidine (1,2,3) were dissolved in 43g. water and 10cc. concentrated hydrochloric acid added. After diazotising with a solution of 3•2g. sodium nitrite in 20cc. water, the clear solution was poured into a solution of 23g. crystalline sodium sulphite in 92g. of water and 7g. 40% sodium hydroxide, cooled directly with 30g. ice. The sulphonate was salted out as before. Yellow leaflets. Yield: 13•3g.

(b) 2,3-di-Methyl-phenylhydrazine sodium sulphonate.

13g. of the above were dissolved in 60cc. hot water and filtered hot. 7·5g. of glacial acetic acid were added and the diazo-compound reduced with 7·5g. zinc dust. After boiling for a short time and filtering, 100cc. saturated salt solution were added. On cooling, white crystals were obtained. Yield: 10·6g.

(c) 2,3-di-Methyl-phenylhydrazine hydrochloride.

10g. of the sodium sulphonate were dissolved in 60cc. hot water and decomposed with 80cc. concentrated hydrochloric acid. The white crystals deposited on cooling were filtered and washed with a little water. (7·8g.). Recrystallisation from alcohol gave white leaflets, m.p. 208° under decomposition.

(d) 2,3-di-Methyl-phenylhydrazine.

On dissolving the hydrochloride in a little hot water and treating with excess concentrated sodium hydroxide solution, the hydrazine was liberated as an oil, which crystallised on cooling. The crystals were filtered off and washed with a little water. Recrystallisation from alcohol gave colourless needles, m.p. 108°. Weight: 3·7g.

(e) N-(2,3-Xylylamino)-2-methyl-4,6-diphenyl-pyridinium iodide.

5·7g. Pyrylium iodide in boiling benzene were treated with a solution of the above hydrazine in benzene, the hydrazine solution being added drop by drop. After two hours refluxing the red iodide was completely decomposed. The pyridinium iodide was filtered cold, washed with benzene and dried. Weight: 6·5g. m.p. 155°. Two recrystallisations from alcohol gave yellow leaflets, m.p. 157°.

Analysis:

Found:- C. 63·37%, H. 5·12%.

Calc. for $C_{26}H_{25}N_2I$:- C. 63·42%, H. 5·08%.

(f) Intramolecular change. Formation of 2-(3',4'-di-methyl-2'-aminobenzyl)-4,6-diphenyl-pyridine.

5g. of the above pyridinium iodide were treated with a mixture of 125cc. alcohol and 10cc. 10% sodium hydroxide solution. The whole was refluxed for about 30 minutes, a little zinc dust added and refluxing continued for a few minutes till the colour was pale yellow. On standing overnight, the liquid deposited crystals (2g.) which were filtered off and washed with a little alcohol. Two recrystallisations from alcohol gave very fine, white needles, m.p. 144·5°.

Analysis:- 4·823mg. gave 15·155mg. CO_2 and 2·890mg. H_2O.

Found:- C. 85·68%, H. 6·66%.

Calc. for $C_{26}H_{24}N_2$:- C. 85·71%, H. 6·59%.

Colour of anhydrobase

(a) In ethyl alcohol — indigo-blue.

(b) In methyl alcohol — blue tinged with violet.

Measurement of velocity of intramolecular change.

1/2,000 Mol. (0·246g.) N-(2,3-xylylamino)-2-methyl-4,6-diphenyl-pyridinium iodide in 20cc. alcohol + 1cc. 2N. NaOH.

(a) Time in ethyl alcohol — 4 minutes.

(b) Time in methyl alcohol — 15·33 minutes.

N-(2,5-Xylylamino)-2-methyl-4,6-diphenyl-pyridinium iodide.

(a) 2,5-di-Methyl-diazobenzene sodium sulphonate.

17·5g. p-Xylidine (1,4,2) were dissolved in 150cc. water and 34cc. concentrated hydrocholoric acid added with constant stirring. The finely suspended hydrochloride was then diazotised with a solution of 11g. of sodium nitrite in 80cc. water. The clear solution was poured into a solution of 80g. crystalline sodium sulphite in 320g. water and 24g. of 35% sodium hydroxide, cooled directly with 100g. ice. The

sulphonic acid salt was obtained by salting out. Yield: 34·5g.

(b) 2,5-di-Methyl-phenylhydrazine sodium sulphonate.

34g. of the above were dissolved in 120cc. hot water and filtered while hot. The yellowish-red filtrate was decolourised by 18g. of glacial acetic acid and 18g. zinc dust. The clear solution was filtered hot and treated with 120cc. saturated salt solution. On cooling, 19·7g. of the hydrazine derivative were obtained.

(c) 2,5-di-Methyl-phenylhydrazine hydrochloride.

19·7g. of the above salt were dissolved in 50cc. hot water and 75cc. concentrated hydrochloric acid added. On cooling, the hydrochloride came down as beautiful white needles. Yield: 15·5g. Recrystallisation from a little water gave small needles, m.p. 206°.

(d) 2,5-di-Methyl-phenylhydrazine.

7g. of the hydrochloride were dissolved in the minimum amount of hot water and treated with concentrated sodium hydroxide solution (1:3) until strongly alkaline. On cooling, the free hydrazine was obtained in the form of fine colourless crystals, m.p. 74°.

(e) N-(2,5-Xylylamino)-2-methyl-4,6-diphenyl-pyridinium iodide.

5g. of pyrylium iodide, suspended in boiling benzene, were treated, drop by drop, with a solution of 3g. of the above hydrazine in benzene. After all the hydrazine solution had been added, the mixture was refluxed for half an hour until the product was completely yellow in colour. On allowing to cool, the pyridinium iodide was filtered, washed with benzene and dried. Weight: 6.1g. m.p. 151°. Recrystallisation from alcohol gave yellow needles, m.p. 153°. The substance was very sensitive to light and darkened rapidly on standing exposed to day-light.

Analysis:

Found:-	C.	63.12%,	H.	5.01%.
Calc. for $C_{26}H_{25}N_2I$:-	C.	63.42%,	H.	5.08%.

(f) Intramolecular change. Formation of 2-(3',6'-di-methyl-2'-amino-benzyl)-4,6-diphenyl-pyridine.

5g. of the above pyridinium iodide were treated with a mixture of 125cc. alcohol and 10cc. 10% sodium hydroxide solution. The violet-blue solution so obtained was refluxed for half an hour, when the colour was reddish-yellow. Treatment with zinc dust further reduced this to pale yellow. On cooling and

filtering, the filtrate deposited fine needles after standing overnight in the ice-chamber. Recrystallisation from alcohol gave very fine white needles, m.p. 154·5°.

Analysis:- 4·773mg. gave 14·985mg. CO_2 and 2·830mg. H_2O.

Found:- C. 85·64%, H. 6·59%.

Calc. for $C_{26}H_{24}N_2$:- C. 85·71%, H. 6·59%.

Colour of anhydrobase.

(a) In ethyl alcohol — indigo-blue

(b) In methyl alcohol — blue tinged with violet.

Measurement of velocity of intramolecular change.

1/2,000 Mol. N-(2,5-xylylamino)-2-methyl-4,6-diphenyl-pyridinium iodide in 20cc. alcohol + 1cc. 2N. NaOH.

(a) Time in ethyl alcohol 5 minutes.

(b) Time in methyl alcohol 19·75 minutes.

N-(3,5-Xylylamino)-2-methyl-4,6-diphenyl-pyridinium iodide.

(a) 3,5-di-Methyl-diazobenzene sodium sulphonate.

10g. of symmetrical meta-xylidine (1,3,5) were dissolved in 86g. water and 20cc. of concentrated hydrochloric acid stirred in. The resulting suspension of the hydrochloride was diazotised with a solution of 6·5g. sodium nitrite in 40cc. water and the clear liquid poured

into a mixture of 46g. hydrated sodium sulphite in 184g. water and 14g. 35% sodium hydroxide, cooled directly with 50g. of ice. The resulting sulphonate was salted out. Yield: 26g.

(b) 3,5-di-Methyl-phenylhydrazine sodium sulphonate.

26g. of the above were dissolved in 90cc. hot water and filtered. The filtrate was reduced with 14g. of glacial acetic acid and 14g. zinc dust. A further 50cc. of hot water was added to the colourless solution to aid filtration and the filtrate treated with 200cc. of saturated salt solution. Yield of hydrazine salt was 13·5g.

(c) 3,5-di-Methyl-phenylhydrazine hydrochloride.

This hydrazine salt was dissolved in 60cc. of hot water and 100cc. of concentrated hydrochloric acid added. On cooling, white crystals of the hydrochloride were obtained. Recrystallisation from water gave small prisms, which showed no definite melting point, decomposing around 130°.

(d) 3,5-di-Methyl-phenylhydrazine.

3g. of the hydrochloride were dissolved in a minimum of hot water and rendered alkaline with concentrated sodium hydroxide solution. On cooling, crystals

of free hydrazine were obtained. Yield: 1·3g. m.p. 79°.

(e) N-(3,5-Xylylamino)-2-methyl-4,6-diphenyl-pyridinium iodide.

1·2g. of the above hydrazine were dissolved in benzene and added, drop by drop, to a suspension of 2g. pyrylium iodide in boiling benzene. Refluxing was continued till the colour of the product was completely yellow. After cooling the new iodide was filtered, washed with benzene and dried. It had m.p. 180°. Recrystallisation from alcohol gave yellow prisms, m.p. 191°. Weight: 1·5g.

Analysis:

Found:-	C.	63·39%,	H.	5·12%.
Calc. for $C_{26}H_{25}N_2I$:-	C.	63·42%,	H.	5·08%.

(f) Intramolecular change. Formation of 2-(4',6'-di-methyl-2'-aminobenzyl)-4,6-diphenyl-pyridine.

0·5g. of the quaternary iodide was treated with a boiling mixture of 20cc. alcohol and 1cc. 2N. sodium hydroxide and refluxed for half an hour. The solution was then light brown in colour. The reddish-brown crystals which separated on cooling were filtered and recrystallised twice from alcohol. Fine white needles were obtained, m.p. 162°.

Analysis:- 4·763mg. gave 14·915mg. CO_2 and 2·850mg. H_2O.

Found:- C. 85·42%, H. 6·65%.

Calc. for $C_{26}H_{24}N_2$:- C. 85·71%, H. 6·59%.

Colour of anhydrobase.

(a) In ethyl alcohol violet-blue.

(b) In methyl alcohol violet tinged with blue.

Measurement of velocity of intramolecular change.

1/2,000 Mol. (0·246g.) N-(3,5-xylylamino)-2-methyl-4,6-diphenyl-pyridinium iodide in 20cc. alcohol + 1cc. 2N. NaOH.

(a) Time in ethyl alcohol 19 minutes.

(b) Time in methyl alcohol 77·5 minutes.

N-(2,4,5-tri-Methyl-phenyl-amino)-2-methyl-4,6-diphenyl-pyridinium iodide.

(a) 2,4,5-tri-Methyl-diazobenzene sodium sulphonate.

19·5g. of pseudo-cumidine were dissolved in 150g. water and 34cc. concentrated hydrochloric acid added. The resulting suspension was diazotised with 11g. sodium nitrite in 80g. water and the clear solution then poured into a mixture of 80g. hydrated sodium sulphite in 320g. water and 24g. 35% sodium hydroxide, cooled directly with 100g. ice. The sulphonate was salted out. Yield: 32g.

(b) 2,4,5-tri-Methyl-phenylhydrazine sodium sulphonate.

32g. of the diazo-salt were dissolved in 150cc. hot water and the filtered solution reduced by means of 17g. glacial acetic acid and 17g. zinc dust. The residual zinc was removed by filtration and the filtrate treated with 200cc. saturated salt solution. Yield: 30g.

(c) 2,4,5-tri-Methyl-phenylhydrazine hydrochloride.

The above was dissolved in 150cc. of water and an equal quantity of concentrated hydrochloric acid added. On cooling, the brownish-white product was filtered off. Weight: 13·5g.

(d) 2,4,5-tri-Methyl-phenylhydrazine.

5g. of the hydrochloride, dissolved in hot water, were boiled with norit and filtered. The filtrate was made alkaline with concentrated sodium hydroxide solution (1:3). On cooling, the precipitated hydrazine was filtered, washed with water and dried. Weight: 3g. Colourless needles, m.p. 120°.

(e) N-(2,4,5-tri-Methyl-phenyl-amino)-2-methyl-4,6-diphenyl-pyridinium iodide.

4g. of pyrylium iodide and 2·5g. of the above hydrazine were refluxed in benzene for an hour. The product, which was completely yellow in colour, was

filtered in the cold, washed with benzene and dried. Weight: 5g., small needles, m.p. 128°. The iodide could not be recrystallised as it decomposed on heating in alcohol giving 2-methyl-4,6-diphenyl-pyridine, (see later).

Analysis:

Found:- C. 64·90%, H. 5·41%.

Calc. for $C_{27}H_{27}N_2I$:- C. 64·02%, H. 5·34%.

(f) Intramolecular change. Formation of 2-(3',5',6'-tri-methyl-2'-amino-benzyl)-4,6-diphenyl-pyridine.

3g. of the pyridinium iodide were treated with a hot solution of 75cc. alcohol and 6cc. 10% sodium hydroxide. After boiling for a few minutes the blue colouration first produced gave way to a light brown colour. On cooling, 1g. of crude product was obtained, m.p. 164°. Two recrystallisations from alcohol gave very fine, small, white needles, m.p. 166°.

Analysis:- 4·910mg. gave 15·415mg. CO_2 and 3·060mg. H_2O.

Found:- C. 85·7%, H. 6·89%.

Calc. for $C_{27}H_{26}N_2$:- C. 85·7%, H. 6·88%.

Colour of anhydrobase.

(a) In ethyl alcohol pure blue.

(b) In methyl alcohol blue.

Measurement of velocity of intramolecular change.

1/2,000 Mol. (0·253g.) N-(2,4,5-tri-methyl-phenyl-amino)-2-methyl-4,6-diphenyl-pyridinium iodide in 20cc. alcohol + 1cc. 2N. NaOH.

(a)	Time in ethyl alcohol	1·3 minutes.
(b)	Time in methyl alcohol	4·8 minutes.

Decomposition of N-(2,4-xylylamino)-2-methyl-4,6-diphenyl-pyridinium iodide and N-(2,4,5-tri-methyl-phenyl-amino)-2-methyl-4,6-diphenyl-pyridinium iodide on attempted recrystallisation.

When an attempt was made to recrystallise N-(2,4,5-tri-methyl-phenyl-amino)-2-methyl-4,6-diphenyl-pyridinium iodide from alcohol, the yellow solution became dark red in colour (iodine) and a test with alkali gave no blue colouration. The solution was accordingly rendered alkaline with sodium hydroxide and the alcohol distilled off in steam, when an oily substance separated. This sticky material was dissolved in alcohol and treated in the heat with an alcoholic solution of picric acid. On allowing to cool, long yellow prisms separated out, m.p. 209°. Recrystallisation from alcohol gave beautiful yellow prisms, m.p. 213°. The melting point corresponds to

that of the picrate of 2-methyl-4,6-diphenyl-pyridine. (c.f. Beilstein. Erstes Ergänzungswerk, Bd. XX/XXII, p. 180).

Attempts to recrystallise the quaternary iodide from other solvents were equally unsuccessful. Glacial acetic acid and acidified alcoholic solutions were also tried. With alcohol and perchloric acid a perchlorate was obtained, m.p. 197-8°.

N-(2,4-Xylylamino)-2-methyl-4,6-diphenyl-pyridinium iodide was found to decompose in a similar manner on heating in alcohol, the solution again becoming reddish in colour. On evaporating to small bulk, crystals came down on cooling, m.p. 205°. These were shown to contain iodine in ionic form. The substance was fairly insoluble in cold water, but dissolved readily on heating. Recrystallisation from alcohol gave yellowish-white needles, m.p. 210°, which became yellow on standing for some time exposed to light. This substance appeared to be the hydriodide of 2-methyl-4,6-diphenyl-pyridine.

Isolation of 2-methyl-4,6-diphenyl-pyridine.

The hydriodide was dissolved in a little hot water and the solution made alkaline with sodium hydroxide. A white powder, practically insoluble in water, was obtained. This was recrystallised from

ligroin and gave m.p. 72-73°. (c.f. Dilthey, J. pr. [2] 94, 74).

Perchlorate.

Treatment of this 2-methyl-4,6-diphenyl-pyridine with perchloric acid in alcohol gave a perchlorate, m.p. 197-8°, identical with that obtained above from N-(2,4,5-tri-methyl-phenyl-amino)-2-methyl-4,6-diphenyl-pyridinium iodide.

N-(p-Chlorophenylamino)-2-methyl-4,6-diphenyl-pyridinium iodide.

(a) p-Chlorophenyl hydrazine.

(1) p-Chloro-diazobenzene sodium sulphonate.

5g. p-Chloro-aniline were dissolved in 38cc. of water and 8·4cc. concentrated hydrochloric acid and diazotised with a solution of 3g. sodium nitrite in 20cc. of water. The clear solution was then poured into a mixture of 20g. crystalline sodium sulphite in 80cc. of water and 6g. 35% sodium hydroxide, cooled directly with 25g. ice. On addition of approximately the same volume of saturated salt solution, the diazo-salt was obtained as a sulphur-yellow precipitate of fine leaflets. The product, after washing with salt solution and water and drying, weighed 9·5g.

(2) p-Chloro-phenylhydrazine sodium sulphonate.

9·5g. of the diazo-salt were dissolved in 60cc. hot water and rapidly filtered. The reddish-yellow filtrate was reduced to a colourless liquid with 5g. glacial acetic acid and 5g. zinc dust. The reduced solution was filtered hot and 60cc. saturated salt solution added. On cooling white crystals of the hydrazine sodium sulphonate were obtained. These were filtered off, washed with water and dried. Beautiful prisms, weight 7·6g.

(3) p-Chloro-phenylhydrazine hydrochloride.

7·6g. of the above were dissolved in 76cc. hot water and 80cc. concentrated hydrochloric acid added to the hot solution. On cooling, the hydrochloride was obtained as almost pure white crystals. These were filtered off and washed with a little dilute hydrochloric acid. Yield: 5·5g.

(4) p-Chloro-phenylhydrazine.

5g. Hydrochloride were dissolved by heating in the minimum amount of water and a 10% sodium hydroxide solution added, drop by drop, till the liquid became alkaline. On cooling, the free hydrazine solidified to small pellets. These were filtered off, well powdered, washed with water and dried between filter-

paper. Weight: 3·3g. Recrystallisation from a little hot water gave needles, m.p. 83°.

(b) N-(p-Chloro-phenylamino)-2-methyl-4,6-diphenyl-pyridinium iodide.

5g. Pyrylium iodide were mixed with 3g. p-chloro-phenylhydrazine and about 60cc. benzene added. The whole was refluxed on a waterbath till the compact crystals formed were completely yellow in colour. On allowing to cool, the new iodide was filtered, washed with benzene and dried. Yield: 6g. m.p. 181°. After three recrystallisations from alcohol beautiful yellow prisms, m.p. 189°, were obtained. The substance was fairly sensitive to light.

Analysis:- 5·354mg. gave 11·345mg. CO_2 and 1·990mg. H_2O.

Found:- C. 57·92%, H. 4·17%.

Calc. for $C_{24}H_{20}N_2I$:- C. 57·8%, H. 4·01%.

(c) Intramolecular change. Formation of 2-(3'-chloro-6'-amino-benzyl)-4,6-diphenyl-pyridine.

2g. of the above pyridinium iodide were dissolved in 50cc. hot alcohol and 5cc. 2N. sodium hydroxide solution added. The red-violet solution was refluxed for three hours on the waterbath and the resulting reddish-yellow colour reduced to light yellow by refluxing for a further ten minutes with a little zinc dust.

The liquid was then filtered and allowed to cool when yellow-red crystals separated. These were washed with alcohol and dried. Weight: 0·9g. m.p. 152°. Four recrystallisations from alcohol with addition of norit gave beautiful white needles, m.p. 167°.

Analysis:- 5·237mg. gave 14·940mg. CO_2 and 2·440mg. H_2O.

Found:- C. 77·8%, H. 5·18%.

Calc. for $C_{24}H_{19}N_2Cl$:- C. 77·74%, H. 5·13%.

(d) Indazole Derivative. 2-[3'-(5'-chloro)-indazolo]-4,6-diphenyl pyridine.

0·5g. of the above product was dissolved in 5cc. hot glacial acetic acid and 10cc. sulphuric acid (1:5) added. The clear yellow solution was cooled in ice and diazotised with 1·5cc. N sodium nitrite. After standing overnight the yellow product was filtered and recrystallised from alcohol, in which it was not very soluble. The small, slightly yellow needles obtained had m.p. 273°. Weight: 0·4g. After three recrystallisations from toluene, with the help of norit, fine white needles were isolated, m.p. 273°.

Analysis:- 4·749mg. gave 13·195mg. CO_2 and 1·820mg. H_2O.

Found:- C. 75·77%, H. 4·26%.

Calc. for $C_{24}H_{16}N_3Cl$:- C. 75·50%, H. 4·19%.

Colour of anhydrobase.

(a) In ethyl alcohol — violet tinged with red.

(b) In methyl alcohol — red tinged with violet.

Measurement of velocity of intramolecular change.

1/2,000 Mol. (0·2493g.) N-(p-chloro-phenylamino)-2-methyl-4,6-diphenyl-pyridinium iodide in 20cc. alcohol + 1cc. 2N. NaOH.

Time in ethyl alcohol 95 minutes.

N-(meta-Chloro-phenylamino)-2-methyl-4,6-diphenyl-pyridinium iodide.

(a) m-Chloro-phenylhydrazine.

(1) m-Chloro-diazobenzene sodium sulphonate.

5g. m-Chloroaniline were poured into 38cc. of water and 8·4cc. concentrated hydrochloric acid added slowly. The fine suspension of hydrochloride so obtained was diazotised with a solution of 3g. sodium sulphite in 20cc. water. The clear diazotised solution was then poured into a mixture of 20g. crystalline sodium sulphite in 80g. water and 6g. 35% sodium hydroxide, cooled directly with 25g. ice. The sulphonate came out only on addition of saturated salt solution. This was filtered off, washed with salt solution and dried on a porous plate. Weight: 9g.

(2) m-Chloro-phenylhydrazine sodium sulphonate.

9g. of the dried diazo-salt were dissolved in 60cc. hot water and rapidly filtered. 5g. glacial acetic acid were then added to the yellow filtrate and the solution decolourised by gradual addition of 5g. zinc dust. The reduced solution was filtered hot and 70cc. concentrated salt solution added to the filtrate. On allowing to cool, white crystals were obtained. Weight: 8g.

(3) m-Chloro-phenylhydrazine hydrochloride.

8g. of the hydrazine sulphonate were dissolved in 50cc. hot water and 60cc. concentrated hydrochloric acid added. On cooling, m-chloro-phenylhydrazine hydrochloride came down in the form of white needles. After filtering and washing with a little dilute hydrochloric acid, the product was dried on a porous plate. Yield: 5g. The compound was recrystallised from water and hydrochloric acid and gave beautiful needles, m.p. 235°.

(4) m-Chloro-phenylhydrazine.

5g. of the hydrochloride were dissolved in a little hot water and treated with caustic soda solution (1:3) till the liquid was strongly alkaline. The oil which separated was extracted with benzene, the benzene solution washed twice with water and dried over anhydrous

sodium sulphate. The benzene solution of free m-chloro-phenylhydrazine thus obtained was used immediately for the next stage.

(b) N-(m-Chloro-phenylamino)-2-methyl-4,6-diphenyl-pyridinium iodide.

5g. of red pyrylium iodide were suspended in about 60cc. of boiling benzene and the above benzene solution of m-chloro-phenylhydrazine allowed to drop in slowly. The red iodide changed gradually into the yellow pyridinium iodide. Refluxing was continued until the product was completely yellow in colour. On allowing to cool, the solid was filtered, washed thoroughly with benzene and dried. Weight: 5·8g. m.p. 187°. It was obtained completely pure after two recrystallisations from alcohol, in the form of beautiful large yellow prisms, m.p. 191°.

Analysis:- 5·208mg. gave 11·030mg. CO_2 and 1·910mg. H_2O.

Found:- C. 57·78%, H. 4·10%.

Calc. for $C_{24}H_{20}N_2ClI$:- C. 57·8%. H. 4·01%.

(c) Intramolecular change. Formation of 2-(3'-chloro-5'-amino-benzyl)-4,6-diphenyl-pyridine.

1g. N-(m-Chloro-phenylamino)-2-methyl-4,6-diphenyl-pyridinium iodide was dissolved in 35cc. alcohol and 2·5cc. 2N. sodium hydroxide solution added. The

violet-red solution was boiled for seven hours on the waterbath under reflux. On cooling, the reddish-brown product was filtered and washed with water. Weight was 0·5g., m.p. 165-7°. The substance was fairly insoluble in alcohol and came out again only after evaporating down to some half the volume. Three recrystallisations with the help of norit gave fine white prisms, m.p. 177°.

Analysis:

Found:-	C.	77·9%,	H.	5·36%.
Calc. for $C_{24}H_{19}N_2Cl$:-	C.	77·74%,	H.	5·13%.

Colour of anhydrobase.

(a) In ethyl alcohol — red, with violet tinge.

(b) In methyl alcohol — carmine-red.

Measurement of velocity of intramolecular change.

1/2,000 Mol. (0·2493g.) N-(m-chloro-phenylamino)-2-methyl-4,6-diphenyl-pyridinium iodide in 20cc. alcohol + 1cc. 2N. NaOH.

Time in ethyl alcohol 370 minutes.

N-(ortho-Chloro-phenylamino)-2-methyl-4,6-diphenyl-pyridinium iodide.

(a) ortho-Chloro-phenylhydrazine.

(1) o-Chloro-diazo-benzene sodium sulphonate.

10g. o-Chloro-aniline were treated with 76g. water and 17cc. concentrated hydrochloric acid. The resulting suspension of the hydrochloride was diazotised with through cooling by a solution of 6g. sodium nitrite in 40cc. water. The clear diazotised solution was poured into a mixture of 40g. crystalline sodium sulphite in 160g. water and 12g. 35% sodium hydroxide, cooled directly by means of 50g. ice. The sulphur-yellow precipitate of the diazo-sodium sulphonate appeared only slowly after addition of approximately an equal volume of saturated salt solution. Yield was only 14g.

(2) o-Chloro-phenylhydrazine sodium sulphonate.

14g. of the above were dissolved in 90cc. hot water and the yellowish-red solution filtered and reduced by means of 7g. glacial acetic acid and 7g. zinc dust. The clear solution was then filtered hot and treated with 120cc. saturated salt solution. On cooling, the hydrazine sodium sulphonate came down as a white mass of crystals. These were filtered, washed with salt solution and dried. Yield: 10g.

(3) o-Chloro-phenylhydrazine hydrochloride.

10g. of this hydrazine salt were dissolved in 30cc. hot water and 30cc. concentrated hydrochloric acid added. In the cold the hydrazine hydrochloride came down as shining leaflets. Weight: 7·8g. Recrystallisation from water and hydrochloric acid gave needles, m.p. 190° under decomposition.

(4) o-Chloro-phenylhydrazine.

4g. of this hydrochloride were dissolved in a minimum of hot water and a concentrated solution of ammonia added, drop by drop, until the liquid was definitely alkaline. An emulsion was obtained which deposited white leaflets of the free hydrazine on cooling. These were filtered, washed thoroughly with water and quickly dried between filter-paper. Weight: 2·2g. Recrystallisation from a little water gave lovely leaflets, m.p. 47-8°.

(b) N-(o-Chloro-phenylamino)-2-methyl-4,6-diphenyl-pyridinium iodide.

4g. of pyrylium iodide, suspended in boiling benzene, were treated with a solution of the above hydrazine in benzene, dropped in slowly from a dropping-funnel. Refluxing was continued till the red iodide had completely disappeared and the product was completely

yellow. This was then filtered off in the cold and washed thoroughly with benzene. The yield of crude product was 5g., m.p. 193°. Two recrystallisations from alcohol gave beautiful yellow prisms, m.p. 195°.

Analysis:- 5·014mg. gave 10·655mg. CO_2, 1·930mg. H_2O and a residue 0·007 mg.

Found:- C. 58·0%, H. 4·3%.

Calc. for $C_{24}H_{20}N_2ClI$:- C. 57·8%, H. 4·0%.

(c) Intramolecular change. Formation of 2-(4'-chloro-5'-amino-benzyl)-4,6-diphenyl-pyridine.

2g. N-(o-Chloro-phenylamino)-2-methyl-4,6-diphenyl-pyridinium iodide were dissolved in 50cc. hot alcohol and 5cc. 2N. sodium hydroxide solution added. The red-violet solution was refluxed for about two hours on the waterbath, then for so long with zinc dust until the colour was light-yellow. The solution was then filtered and allowed to stand overnight in the ice-chamber. The product was mainly crystalline. The super-natant liquid was decanted off, the brownish-red crystals being scraped out and dried on filter-paper. Weight: 0·7g., m.p. 106°. After four recrystallisations from alcohol, in which the substance was fairly soluble, practically colourless prisms were obtained, m.p. 108°.

Analysis:- 5·084mg. gave 14·500mg. CO_2, 2·470mg. H_2O and 0·007mg. residue.

Found:- C. 77·77%, H. 5·39%.

Calc. for $C_{24}H_{19}N_2Cl$:- C. 77·74%, H. 5·13%.

Colour of anhydrobase.

(a) In ethyl alcohol violet-red.

(b) In methyl alcohol wine-red.

Measurement of velocity of intramolecular change.

1/2,000 Mol. (0·2493g.) N-(o-chloro-phenylamino)-2-methyl-4,6-diphenyl-pyridinium iodide in 20cc. alcohol + 1cc. 2N. NaOH.

Time in ethyl alcohol 36 minutes.

(a) N-(p-Bromo-phenylamino)-2-methyl-4,6-diphenyl-pyridinium iodide.

The conversion into the pyridinium compound can be carried out in alcohol, benzene or glacial acetic acid solution. Benzene was used in this case.

3g. of red pyrylium iodide were mixed with 2·5g. p-bromo-phenylhydrazine (excess) and 60cc. benzene added. Upon warming on the waterbath the red iodide appeared to go into solution, the colour becoming dark red. From this solution, yellow crystals were gradually deposited. Heating was continued till the product was

completely yellow in colour. The yield of crude quaternary iodide amounted to 3·5g. The substance was purified by recrystallisation from glacial acetic acid and alcohol. Heating too vigorously brought about decomposition. The product was obtained in the form of beautiful yellow needles, m.p. 199°. It was soluble with difficulty in alcohol and benzene, more easily, on the other hand, in glacial acetic acid, acetone and chloroform.

(b) Intramolecular change. Formation of 2-(2'-bromo-5'-amino-benzyl)-4,6-diphenyl-pyridine.

3g. N-(p-Bromo-phenylamino)-2-methyl-4,6-diphenyl-pyridinium iodide were dissolved by boiling with 300cc. alcohol and 15cc. 2N. sodium hydroxide solution added. The red-violet solution was refluxed for five hours on the waterbath, after which time it was reddish-yellow in colour. After heating for a short time with a little zinc dust, the brownish-yellow solution was filtered and allowed to cool. 1·3g. of brownish-red crystals separated. Concentration of the mother-liquid gave a further 0·5g. After several recrystallisations from alcohol with addition of norit, fine, long, white needles were obtained, m.p. 165°.

Analysis:- 4·992mg. gave 12·655mg. CO_2 and 1·990mg. H_2O.

Found:- C. 69·17%, H. 4·58%.

Calc. for $C_{24}H_{19}N_2Br$:- C. 69·39%, H. 4.43%.

Colour of anhydrobase.

(a) In ethyl alcohol — red-violet.

(b) In methyl alcohol — wine-red, tinged with violet.

Measurement of velocity of intramolecular change.

1/2,000 Mol. (0·2715g.) N-(p-bromo-phenylamino)-2-methyl-4,6-diphenyl pyridinium iodide in 20cc. alcohol + 1cc. 2N. NaOH.

Time in ethyl alcohol 152 minutes.

(c) Indazole derivative. 2-[3'-(5'-bromo)-indazolo]-4,6-diphenyl-pyridine.

0·5g. of the above product was dissolved in 5cc. hot glacial acetic acid and 10cc. sulphuric acid (1:5) added. The solution was cooled in ice below +5° and diazotised with a solution of 1·5cc. N. sodium nitrite. On allowing the diazotised solution to stand overnight a yellow amorphous substance was obtained. This was dissolved in a minimum of hot alcohol, and, on allowing to cool, white needles of an indazole derivative were deposited. Recrystallisation from toluene gave very fine, white needles, m.p. 275°.

Analysis:

Found:- C. 67·05%, H. 3·74%.

Calc. for $C_{24}H_{16}N_3Br$:- C. 67·61%, H. 3·75%.

N-(p-Iodo-phenylamino)-2-methyl-4,6-diphenyl-pyridinium iodide.

(a) p-Iodo-phenylhydrazine.

(1) p-Iodo-diazobenzene sodium sulphonate.

8g. p-Iodo-aniline were stirred into 40cc. water and 17cc. concentrated hydrochloric acid and the resulting suspension of the hydrochloride diazotised with a solution of 5·4g. sodium nitrite in 40cc. water. The clear diazotised solution was then poured into a mixture of 40g. crystalline sodium sulphite in 160g. water and 12g. 35% sodium hydroxide, cooled directly with 50g. ice. The sulphonic acid salt was precipitated by the addition of about the same volume of saturated salt solution. It was filtered off, washed with salt solution and dried on a porous plate. Weight: 14g.

(2) p-Iodo-phenylhydrazine hydrochloride.

The diazo-salt proved to be fairly difficultly soluble in water. A hot, reddish-yellow aqueous solution was reduced with 5g. glacial acetic acid and 5g. of zinc dust and filtered hot. To a portion of the

filtrate saturated salt solution was added, but no precipitate of hydrazine sodium sulphonate resulted. From this solution it was also found to be impossible to precipitate the hydrochloride by addition of concentrated hydrochloric acid. This only brought down sodium chloride. When the rest of the filtrate above was treated with concentrated hydrochloric acid directly, the required p-iodo-phenylhydrazine hydrochloride came down, on cooling, as a white mass of crystals. This was purified by solution in water and reprecipitation with concentrated hydrochloric acid.

(3) p-Iodo-phenylhydrazine.

2g. p-Iodo-phenylhydrazine hydrochloride were dissolved in a little warm water and concentrated sodium hydroxide solution added, drop by drop, till the solution was strongly alkaline. The free hydrazine obtained on cooling was filtered and washed thorougly with water. Yield: 1•2g. Recrystallisation from a little water gave white needles, m.p. 103°.

(b) N-(p-Iodo-phenylamino)-2-methyl-4,6-diphenyl-pyridinium iodide.

1•5g. Pyrylium iodide were mixed with 1•2g. p-iodo-phenylhydrazine and 30cc. of benzene added. The mixture was refluxed for four hours on a waterbath.

The whole went slowly into solution and yellow crystals were slowly deposited. After cooling, the yellow iodide was filtered, washed with benzene and dried. Yield: 1·7g. m.p. 168-9°. Three recrystallisations from alcohol gave fine, yellow needles, m.p. 185°.

Analysis:- 4·895mg. gave 8·805mg. CO_2 and 1·750mg. H_2O.

Found:- C. 49·06%, H. 3·97%.

Calc. for $C_{24}H_{20}N_2I_2$:- C. 48·81%, H. 3·4 %.

(c) Intramolecular change. Formation of 2-(2'-iodo-5'-amino-benzyl)-4,6-diphenyl-pyridine.

0·3g. N-(p-Iodo-phenylamino)-2-methyl-4,6-diphenyl-pyridinium iodide were dissolved in 20cc. boiling alcohol and 1cc. of 2N. sodium hydroxide solution added. The red-violet solution was refluxed for four hours on the waterbath. The decolourised solution deposited reddish-yellow crystals, m.p. 160-1°, on cooling. The weight of crude product was 0·15g. Three recrystallisations from alcohol with addition of norit gave almost white prisms, m.p. 164°.

Analysis:- 4·286mg. gave 9·845mg. CO_2, 1·720mg. H_2O and 0·012mg. residue.

Found:- C. 62·64%, H. 4·46%.

Calc. for $C_{24}H_{19}N_2I$:- C. 62·35%, H. 4·12%.

Colour of anhydrobase.

(a)	In ethyl alcohol	red-violet.
(b)	In methyl alcohol	wine-red, with violet tinge.

Measurement of velocity of intramolecular change.

1/2,000 Mol. (0·295g.) N-(p-iodo-phenylamino)-2-methyl-4,6-diphenyl-pyridinium iodide in 20cc. alcohol + 1cc. 2N. NaOH.

Time in ethyl alcohol 175 minutes.

Attempted formation of N-(2',6'-xylylamino)-2-methyl-4,6-diphenyl-pyridinium iodide.

(a) 2,6-di-Methyl-phenylhydrazine.

(1) 2,6-di-Methyl-diazobenzene sodium sulphonate.

17·5g. m-Xylidine (1,3,2) were mixed with 165cc. water and 16·5g. concentrated hydrochloric acid added gradually. The fine crystalline hydrochloride was diazotised with a solution of 11g. sodium nitrite in 80g. water and the clear diazotised solution poured into a mixture of 80g. crystalline sodium sulphite in 320g. water and 24g. 35% sodium hydroxide, cooled directly with 100g. ice. On salting out, 20g. of diazo-sodium sulphonate were obtained.

(2) 2,6-di-Methyl-phenylhydrazine hydrochloride.

20g. of the above were dissolved in 70cc. of hot water and filtered. The filtrate was reduced with 10g. of glacial acetic acid and 10g. of zinc dust. The decolourised solution was filtered hot and treated with 100cc. concentrated hydrochloric acid. On cooling, white needles of the hydrochloride were obtained.
Yield: 8g.

(3) 2,6-di-Methyl-phenylhydrazine.

8g. of the hydrazine hydrochloride were dissolved in a minimum of hot water and the solution made alkaline with concentrated ammonia solution. The oil which separated solidified to starry crystals on cooling. These were filtered off, and washed thoroughly with water. Recrystallisation from a little low-boiling ligroin gave white, shining needles, m.p. 46°.
Yield: 4·5g.

(b) N-(2',6'-Xylylamino)-2-methyl-4,6-diphenyl-pyridinium iodide.

All attempts to prepare this substance by treatment of 2-methyl-4,6-diphenyl-pyrylium iodide with the above 2,6-di-methyl-phenylhydrazine were completely unsuccessful. Attempts were made in benzene, glacial acetic acid, alcoholic acetic acid, alcohol, ether and

alcohol-ether mixtures. It was concluded that the difficulty in condensation was possibly due to steric hindrance, or to a spontaneous decomposition of the primary condensation product.

N-Methyl-phenyl-amino-2-methyl-4,6-diphenyl-pyridinium iodide.

$(CH_3)(C_6H_5)_2C_5H_2N(I)N(CH_3)(C_6H_5)$

(c.f. Süssenguth. Dissertation, Jena, 1922).

The conversion of pyrylium iodide with methyl-phenylhydrazine went very badly in benzene. Part of the product went into solution and deposited small yellow needles on cooling, but the main amount remained as a dark-red sticky mass on the bottom of the flask. On the other hand, the conversion to the pyridinium compound went easily in alcoholic solution.

15g. red pyrylium iodide were heated with 100cc. alcohol to boiling and 5g. methyl-phenylhydrazine in alcohol added slowly. The reaction mixture was then refluxed on the waterbath till all had gone into solution. The contents of the flask were allowed to cool and were set aside for twenty-four hours, when beautiful orange-yellow crystals, m.p. 167°, were found to have been deposited. Weight: 18g. The product was pure, since further recrystallisation failed to raise the

melting point.

The pyridinium iodide was easily soluble in alcohol, chloroform, acetone and acetic acid. The action of sodium acetate and dilute sodium hydroxide gave a yellow flocculent precipitate.

Attempted intramolecular change. Formation of a beta-hydrazide by hydrolysis.

(a) (c.f. Nitzche. Dissertation, Jena, 1924).

An alcoholic solution of the above pyridinium iodide was treated with sodium hydroxide and the anhydro-base which immediately separated allowed to stand for some hours in contact with the solution. Part of the base resinified and settled as sticky lumps on the bottom of the flask. The remainder formed a substance, which came down in white needles. Recrystallisation from alcohol gave lovely, white needle-shaped crystals, m.p. 105°.

(b) A small amount, (2g.), of the iodide was dissolved in hot alcohol and 10cc. 2N. sodium hydroxide added. The mixture was refluxed for three hours on the waterbath. The product was a sticky mass, similar to that described above. Recrystallisation from alcohol gave beautiful, white, crystalline needles, m.p. 105°, the substance being identical to that isolated by Nitzche.

Reformation of the quaternary iodide.

When this substance was dissolved in dilute acetic acid and a few drops of potassium iodide solution added, the original pyridinium iodide, m.p. 167°, was again formed.

Formation of a hydrazide hydrazone.

An alcoholic solution of the same substance was boiled with a little glacial acetic acid and a few drops of phenyl hydrazine, then water added, till a turbidity was obtained. A yellow crystalline substance was precipitated, which dissolved with a deep-blue colour in concentrated sulphuric acid, this giving place to a red substance on addition of water, a reaction typical of hydrazide hydrazones.

The colourless product (m.p. 105°) therefore appeared to be the beta-hydrazide of the yellow anhydrobase, formed by a splitting of the pyridine ring. In this case, therefore, the anhydrobase does not undergo the intramolecular change shown to be typical of the mono-substituted N-amino-pyridinium iodides. Rather part of the anhydrobase polymerises to give a sticky, reddish-brown mass, while a small amount undergoes hydrolysis, involving the breaking open of the pyridine ring and the formation of a beta-hydrazide.

N-Diphenylamino-2-methyl-4,6-diphenyl-pyridinium iodide.

$(CH_3)(C_6H_5)_2C_5H_2N(I)N(C_6H_5)_2$

(c.f. Süssenguth. Dissertation, Jena, 1922).

An attempt to prepare this compound by treatment of the pyrylium compound with di-phenylhydrazine in benzene resulted in the formation of a sticky oil, which could not be induced to crystallise. From alcohol and glacial acetic acid no precipitate was obtained. In ether, a dark oil was again isolated. The reaction was found to proceed smoothly in a mixture of alcohol and ether.

3g. Pyrylium iodide were suspended in 50cc. of an alcohol-ether mixture (2/3 ether and 1/3 alcohol) and 2g. diphenyl-hydrazine added. On warming for one hour on the waterbath, the red iodide disappeared and compact yellow crystals formed. The yield was 4·3g. The compound was recrystallised by dissolving in a little alcohol and adding an equal quantity of ether. Crystallisation was induced by scratching with a glass rod. The substance had m.p. 137°.

Attempted intramolecular change. Formation of anhydrobase and polymerisation product.

(a) c.f. Süssenguth.

An alcoholic solution of this pyridinium iodide,

treated with dilute sodium hydroxide solution gave a yellow amorphous precipitate of the anhydrobase, which, if immediately isolated, readily dissolved in acids and ether. The base was more stable than the corresponding base from methyl-phenylhydrazine, but polymerised in a short time to a dirty yellow substance. It gave a violet colouration with carbon disulphide in the freshly precipitated condition, but none in the polymerised state.

(b) 1g. of the pyridinium iodide was dissolved in 25cc. hot alcohol and 5cc. 2N. sodium hydroxide added. The mixture was refluxed for three hours and allowed to cool. The product was rather oily until completely cold, when a dirty yellow amorphous substance was obtained. It melted between 50° and 60°. Recrystallisation from a number of solvents was tried, but even from the most likely the substance came out either unchanged in the amorphous form or as a sticky oil. On attempting to re-form the original pyridinium iodide by dissolving the substance in a little dilute acetic acid and adding a few drops of potassium iodide solution, no quaternary iodide was obtained, the substance being reprecipitated as an amorphous powder.

Again, therefore, the anhydrobase does not undergo the normal intramolecular change, but polymerises completely to a dark yellow amorphous product. In this case, no beta-hydrazide was observed.

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